PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/14, 409/14, A61K 31/445 A1

(11) International Publication Number: WO 97/18202

(43) International Publication Date: 22 May 1997 (22.05.97)

(21) International Application Number: PCT/GB96/02765

(22) International Filing Date: 13 November 1996 (13.11.96)

(30) Priority Data:
9523460.5 16 November 1995 (16.11.95) GB

(71) Applicant (*for all designated States except US*): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CASTRO PINEIRO, Jose Luis [ES/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). COLLINS, Ian, James [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MACLEOD, Angus, Murray [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MOYES, Christopher, Richard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ROWLEY, Michael [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SHOWELL, Graham, Andrew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

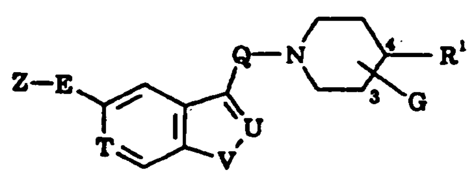
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUBSTITUTED PIPERIDINE DERIVATIVES AS SELECTIVE AGONISTS OF 5-HT RECEPTORS

(57) Abstract

A compound of formula (I), or a salt or prodrug thereof, wherein G is attached at position 3 or 4 of the piperidine ring and represents halogen or C_{1-6} alkoxy; R^1 represents C_{3-6} alkenyl, C_{3-6} alkynyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; processes for its preparation and its use in therapy, particularly in the treatment of migraine.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

SUBSTITUTED PIPERIDINE DERIVATIVES AS SELECTIVE AGONISTS OF 5-HT RECEPTORS

The present invention relates to a class of substituted piperidine derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

It has been known for some time that 5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity are of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1, 1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development Research*, 1992, **26**, 235-240).

The human 5-HT_1-like or 5-HT_{1D} receptor has recently been shown by molecular cloning techniques to exist in two distinct subtypes. These subtypes have been termed 5-HT_{1D_α} (or 5-$HT_{1D\text{-}1}$) and 5-HT_{1D_β} (or 5-$HT_{1D\text{-}2}$), and their amino acid sequences are disclosed and claimed in WO-A-91/17174.

The 5-HT_{1D_α} receptor subtype in humans is believed to reside on sensory terminals in the dura mater. Stimulation of the 5-HT_{1D_α} subtype inhibits the release of inflammatory neuropeptides which are thought to contribute to the headache pain of migraine. The human 5-HT_{1D_β} receptor subtype, meanwhile, is located predominantly on the blood vessels and in the brain, and hence may play a part in mediating constriction of cerebral and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan (GR43175) to humans is known to give rise at therapeutic doses to certain adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med. J.*, 1992, **304**, 1415; J.P. Ottervanger *et al.*, *The Lancet*, 1993, **341**, 861-2; and D.N. Bateman, *The Lancet*, 1993, **341**, 221-4). Since sumatriptan barely discriminates between the human 5-HT_{1D_α} and 5-HT_{1D_β} receptor

subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels with which the 5-HT_{1D_β} subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT_{1D_β} receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 3666-9) that compounds which can interact selectively with the 5-HT_{1D_α} receptor subtype, whilst having a less pronounced action at the 5-HT_{1D_β} subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT_{1D_α} receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent applications 0438230, 0494774 and 0497512, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT_1-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the piperidine derivatives provided by the present invention.

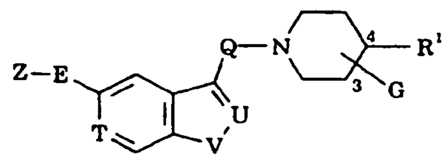
In EP-A-0548813 is described a series of alkoxypyridin-4-yl and alkoxypyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion in EP-A-0548813 of replacing the substituted piperazine moiety with a differently substituted piperidine moiety.

WO-A-91/18897 describes a class of tryptamine derivatives substituted by various five-membered rings, which are stated to be specific to a particular type of "5-HT_1-like" receptor and thus to be effective agents for the treatment of clinical conditions, particularly migraine, requiring this activity. A further class of tryptamine derivatives with alleged anti-migraine activity is disclosed in WO-A-94/02460. However, neither WO-A-91/18897 nor WO-A-94/02460 discloses or suggests the piperidine derivatives provided by the present invention.

Moreover, nowhere in the prior art mentioned above is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a $5\text{-HT}_{1D\alpha}$ receptor binding affinity (IC_{50}) below 50 nM and at least a 10-fold selective affinity for the $5\text{-HT}_{1D\alpha}$ receptor subtype relative to the $5\text{-HT}_{1D\beta}$ subtype.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human $5\text{-HT}_{1D\alpha}$ receptor binding affinity (IC_{50}) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human $5\text{-HT}_{1D\alpha}$ receptor subtype relative to the $5\text{-HT}_{1D\beta}$ subtype. Moreover, the compounds in accordance with this invention possess interesting properties in terms of their efficacy and/or bioavailability.

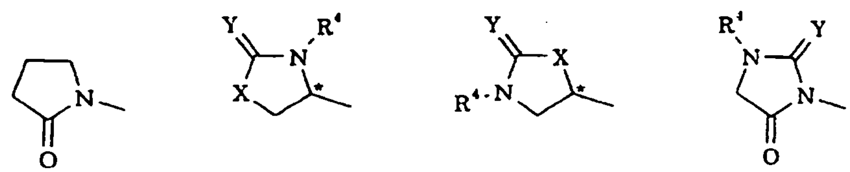
The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, $-OR^5$, $-OCOR^5$, $-OCONR^5R^6$, $-OCH_2CN$, $-OCH_2CONR^5R^6$, $-SR^5$, $-SOR^5$, $-SO_2R^5$, $-SO_2NR^5R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, or a group of formula (Za), (Zb), (Zc) or (Zd):



(Za) (Zb) (Zc) (Zd)

in which the asterisk * denotes a chiral centre; or

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

X represents oxygen, sulphur, -NH- or methylene;

Y represents oxygen or sulphur;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

U represents nitrogen or C-R^2;

V represents oxygen, sulphur or N-R^3;

G is attached at position 3 or 4 of the piperidine ring and represents halogen or C_{1-6} alkoxy;

R^1 represents C_{3-6} alkenyl, C_{3-6} alkynyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^2, R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl; and

R^5 and R^6 independently represent hydrogen, C_{1-6} alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl group; or R^5 and R^6, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring.

Where Z in the compounds of formula I above represents a five-membered heteroaromatic ring, this ring may be optionally substituted by one or, where possible, two substituents. As will be appreciated, where Z represents an oxadiazole, thiadiazole or tetrazole ring, only one substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring Z. Examples of suitable substituents on the five-membered heteroaromatic ring Z include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano and trifluoromethyl.

The group R^1 may be optionally substituted by one or more substituents, as also may the groups R^5 or R^6 where these represent aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl. R^1 may be unsubstituted. R^1 may be substituted Where R^1, R^5 or R^6 represents aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any optional substitution will suitably be on the aryl or heteroaryl moiety thereof, although substitution on the alkyl moiety

thereof is an alternative possibility. Examples of optional substituents thereon include halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C_{1-6} alkyl-tetrazolyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylaminomethyl, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, N-(C_{1-6})alkyl-N-(C_{2-6})alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl, di(C_{1-6})alkylaminosulphonyl, aminosulphonylmethyl, C_{1-6} alkylaminosulphonylmethyl and di(C_{1-6})alkylaminosulphonylmethyl.

When R^5 and R^6, when linked through a nitrogen atom, together represent the residue of an azetidine, pyrrolidine, piperidine, morpholine or piperazine ring, this ring may be unsubstituted or substituted by one or more substituents. Examples of suitable substituents include C_{1-6} alkyl, aryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl and C_{1-6} alkylaminocarbonyl. Typical substituents include methyl, benzyl, methoxy, methoxycarbonyl, ethoxycarbonyl and methylaminocarbonyl. In particular, where R^5 and R^6 together represent the residue of a piperazine ring, this ring is preferably substituted on the distal nitrogen atom by a C_{2-6} alkoxycarbonyl moiety such as methoxycarbonyl or ethoxycarbonyl.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio" and "C_{1-6} alkylamino" are to be construed accordingly.

The expression "C_{2-6} alkenyl" as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl, dimethylallyl and butenyl groups.

The expression "C_{2-6} alkynyl" as used herein refers to straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Typical aryl groups include phenyl and naphthyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl. As mentioned above the alkyl group may be straight or branched.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridylmethyl, pyridylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolylmethyl and isoquinolylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their

pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard. Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. For example, the compounds of formula I above wherein Z represents a group of formula (Zb) or (Zc) have a chiral centre denoted by the asterisk *, which may accordingly be in the (*R*) or (*S*) configuration. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

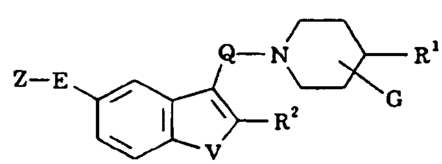
Where E and Q, which may be the same or different, represent straight or branched alkylene chains, these may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or

butylene. In addition, the alkylene chain Q may be substituted in any position by one or more substituents selected from fluoro and hydroxy giving rise, for example, to a 2-hydroxypropylene, 2-hydroxymethyl-propylene, 2-fluoropropylene or 2-fluoromethyl-propylene chain Q. Moreover, E may represent a chemical bond such that the moiety Z is attached directly to the central fused bicyclic heteroaromatic ring system containing the variables T, U and V.

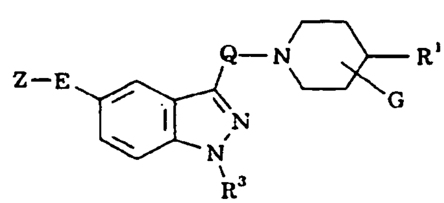
Suitably, E represents a chemical bond or a methylene linkage.

Representative alkylene chains for Q include propylene, butylene, 2-hydroxypropylene, 2-hydroxymethyl-propylene, 2-fluoropropylene and 2-fluoromethyl-propylene, especially propylene.

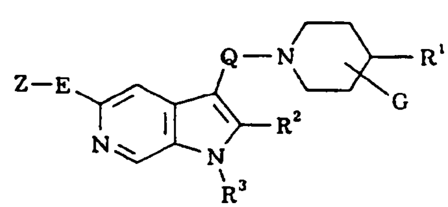
The compound of formula I in accordance with the present invention is suitably an indole, benzofuran or benzthiophene derivative of formula IA, an indazole derivative of formula IB, or a pyrrolo[2,3-c]pyridine derivative of formula IC:



(IA)

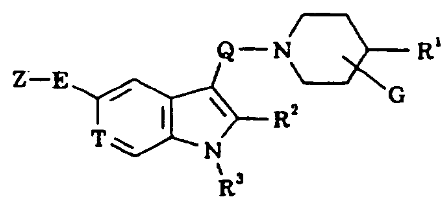


(IB)



(IC)

wherein Z, E, Q, V, G, R^1, R^2 and R^3 are as defined above. Preferably, the compounds according to the invention are indole or pyrrolo[2,3-c]pyridine derivatives of formula ID:



(ID)

wherein Z, E, Q, T, G, R^1, R^2 and R^3 are as defined above, in particular wherein R^2 and R^3 are both hydrogen.

Suitable values for the substituent R^1 include allyl, dimethylallyl, butenyl, propargyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, thienylmethyl, furylethyl, thienylethyl, imidazolylmethyl and pyridylmethyl; alternatively allyl, dimethylallyl, butenyl, propargyl, benzyl, phenylethyl, phenylpropyl, furylmethyl, thienylmethyl, imidazolylmethyl and pyridylmethyl, any of which groups may be optionally substituted by one or more substituents selected typically from halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C_{1-6} alkyl-tetrazolyl, C_{1-6} alkoxy, amino, di(C_{1-6})alkylamino, di(C_{1-6})alkylaminomethyl, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, N-(C_{1-6})alkyl-N-(C_{2-6})alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, aminocarbonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, di(C_{1-6})alkylaminosulphonyl and C_{1-6} alkylaminosulphonylmethyl.

Particular values of R^1 include allyl, dimethylallyl, butenyl, propargyl, benzyl, fluorobenzyl, difluorobenzyl, cyanobenzyl, tetrazolyl-benzyl, methyltetrazolyl-benzyl, methoxybenzyl, aminobenzyl, dimethylaminomethyl-benzyl, acetylamino-benzyl, aminocarbonyl-benzyl, methylaminocarbonyl-benzyl, dimethylaminocarbonyl-benzyl, aminosulphonyl-benzyl, dimethylaminosulphonyl-benzyl, trifluoromethyl-

benzyl, phenylethyl, fluoro-phenylethyl, difluoro-phenylethyl, trifluoromethyl-phenylethyl, cyano-phenylethyl, methoxy-phenylethyl, triazolyl-phenylethyl, amino-phenylethyl, dimethylamino-phenylethyl, acetylamino-phenylethyl, methoxycarbonylamino-phenylethyl, (N-methyl-N-methoxycarbonyl)amino-phenylethyl, aminocarbonylamino-phenylethyl, fluoro(phenyl)propyl, phenylpropyl, furylmethyl, thienylmethyl, furylethyl, thienylethyl, imidazolylmethyl, pyridylmethyl and amino-pyridylmethyl; other values are allyl, dimethylallyl, butenyl, propargyl, benzyl, fluorobenzyl, difluorobenzyl, cyanobenzyl, tetrazolyl-benzyl, methyltetrazolyl-benzyl, methoxybenzyl, aminobenzyl, dimethylaminomethyl-benzyl, acetylamino-benzyl, aminocarbonyl-benzyl, methylaminocarbonyl-benzyl, dimethylaminocarbonyl-benzyl, aminosulphonyl-benzyl, dimethylaminosulphonyl-benzyl, phenylethyl, fluoro-phenylethyl, difluoro-phenylethyl, trifluoromethyl-phenylethyl, cyano-phenylethyl, triazolyl-phenylethyl, amino-phenylethyl, dimethylamino-phenylethyl, acetylamino-phenylethyl, methoxycarbonylamino-phenylethyl, (N-methyl-N-methoxycarbonyl)amino-phenylethyl, aminocarbonylamino-phenylethyl, phenylpropyl, furylmethyl, thienylmethyl, imidazolylmethyl, pyridylmethyl and amino-pyridylmethyl.

Suitably, R^2 and R^3 independently represent hydrogen or methyl, especially hydrogen.

Suitably, R^4 represents hydrogen or methyl, especially hydrogen.

Suitably, R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, trifluoromethyl, phenyl, methylphenyl (especially 4-methylphenyl), benzyl and phenethyl.

In the compounds of formula I above, the substituent G suitably represents fluoro or methoxy.

Suitably, the substituent Z represents hydrogen, fluoro, cyano, hydroxy, methoxy, ethoxy, benzyloxy, methylamino-carbonyloxy, cyano-methoxy, aminocarbonyl-methoxy, methylsulphonyl, aminosulphonyl, N-

methylamino-sulphonyl, N,N-dimethylamino-sulphonyl, amino, formylamino, acetylamino, trifluoromethyl-carbonylamino, benzyloxy-carbonylamino, methyl-sulphonylamino, ethyl-sulphonylamino, methylphenyl-sulphonylamino, N-methyl-(N-methylsulphonyl)-amino, N-methyl-(N-ethylsulphonyl)-amino, N-methyl-(N-trifluoromethylsulphonyl)-amino, N-ethyl-(N-methylsulphonyl)-amino, N-benzyl-(N-methylsulphonyl)-amino, N-benzyl-(N-ethylsulphonyl)-amino, acetyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, butylaminocarbonyl, benzylaminocarbonyl or phenethyl-aminocarbonyl; or a group of formula (Za), (Zb), (Zc) or (Zd) as defined above; or an optionally substituted five-membered heteroaromatic ring as specified above.

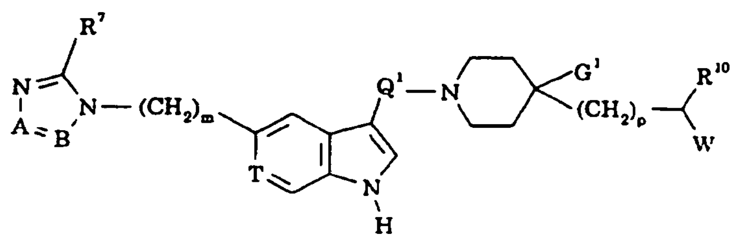
In a particular embodiment, Z represents $-SO_2NR^5R^6$ in which R^5 and R^6 are as defined above. In a subset of this embodiment, R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl, especially hydrogen or methyl. Particular values of Z in this context include aminosulphonyl, N-methylamino-sulphonyl and N,N-dimethylamino-sulphonyl, especially N-methylamino-sulphonyl.

In another embodiment, Z represents a group of formula (Zb) in which R^4 is hydrogen or methyl. In a subset of this embodiment, X and Y both represent oxygen. In a particular aspect of this subset, the chiral centre denoted by the asterisk * is in the (*S*) configuration.

When the group Z represents an optionally substituted five-membered heteroaromatic ring, this is suitably a 1,3-oxazole, 1,3-thiazole, imidazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring. Preferably, the ring is a 1,3-oxazole, 1,3-thiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole or 1,2,4-triazole ring, in particular a 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl moiety.

Suitably, the five-membered heteroaromatic ring Z is unsubstituted. Examples of optional substituents which may typically be attached to the moiety Z include methyl, ethyl, benzyl and amino.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

m is zero, 1, 2 or 3, preferably zero or 1;

p is zero, 1 or 2;

Q^1 represents a straight or branched alkylene chain containing from 2 to 5 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

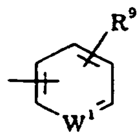
G^1 represents fluoro or methoxy;

A represents nitrogen or CH;

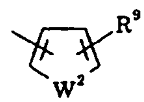
B represents nitrogen or C-R^8;

R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl;

W represents a group of formula (Wa), (Wb) or (Wc):

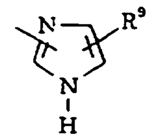


(Wa)



(Wb)

,



(Wc)

in which

W^1 represents CH or nitrogen;

W^2 represents oxygen, sulphur, NH or N-methyl;

R^9 represents hydrogen, halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C_{1-6} alkyl-tetrazolyl, C_{1-6} alkoxy, C_{2-6} alkylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylaminomethyl, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonyl, aminosulphonyl, di(C_{1-6})alkylaminosulphonyl or C_{1-6} alkylaminosulphonylmethyl; and

R^{10} represents hydrogen or C_{1-3} alkyl optionally substituted by halogen.

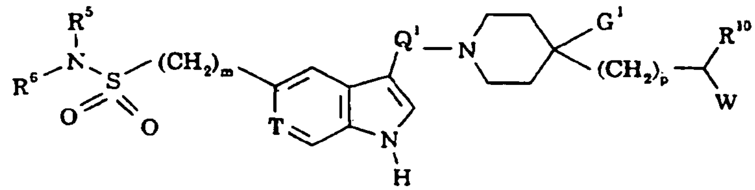
Suitably, Q^1 represents a straight or branched 3 or 4 carbon alkylene chain, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy. Particular alkylene chains for Q^1 include propylene, butylene, 2-hydroxypropylene, 2-(hydroxymethyl)-propylene, 2-fluoropropylene and 2-(fluoromethyl)-propylene, especially propylene.

Particular values of R^7 and R^8 include hydrogen, methyl, ethyl, benzyl and amino, especially hydrogen.

Particular values of R^9 include hydrogen, fluoro, cyano. triazolyl, tetrazolyl, methyl-tetrazolyl, methoxy, amino, dimethylaminomethyl, acetylamino, aminocarbonylamino, methylaminocarbonyl, aminosulphonyl and dimethylaminosulphonyl, especially hydrogen or fluoro.

Particular values of R^{10} include hydrogen and C_{1-3} alkyl, for example hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

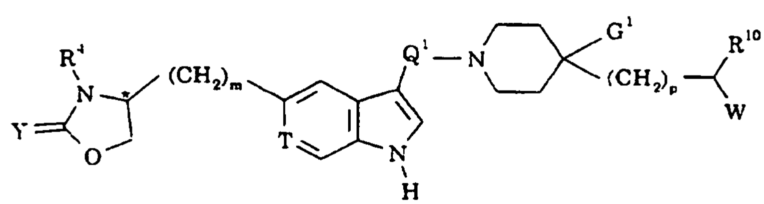
wherein

m, p, Q^1, T, G^1, W and R^{10} are as defined with reference to formula IIA above; and

R^5 and R^6 are as defined with reference to formula I above.

Particular values of R^5 and R^6 in relation to formula IIB above include hydrogen and C_{1-6} alkyl, especially hydrogen or methyl. Suitably, one of R^5 and R^6 represents hydrogen and the other represents hydrogen or methyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein the asterisk * denotes a chiral centre;

m, p, Q^1, T, G^1, W and R^{10} are as defined with reference to formula IIA above; and

R^4 and Y are as defined with reference to formula I above.

Particular values of R^4 in relation to formula IIC include hydrogen and methyl.

Preferably, Y in formula IIC is oxygen.

Preferably, the chiral centre denoted by the asterisk * in formula IIC is in the (*S*) configuration.

Specific compounds within the scope of the present invention include:

4-benzyl-4-fluoro-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-[2-(3-fluorophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-(3-fluorobenzyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-(2-fluorobenzyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-benzyl-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-benzyl-4-methoxy-1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]piperidine;

4-(2-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(3-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(4-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-[2-(trifluoromethyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(N,N-dimethylaminosulfonyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-(2-phenylpropyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[3-fluoro-(2-phenyl)propyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(4-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-(2-phenylethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-thienyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-[2-(2-cyanophenyl)ethyl]-4-fluoro-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(3-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(3-thienyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid

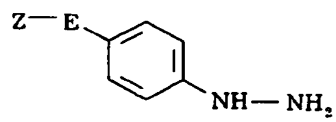
compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for

aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

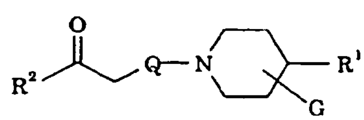
In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention wherein T represents CH, U represents C-R^2 and V represents N-R^3, corresponding to the indole derivatives of formula ID as defined above wherein T represents CH, may be prepared by a process which comprises reacting a compound of formula III:



(III)

wherein Z and E are as defined above; with a compound of formula IV, or a carbonyl-protected form thereof:



(IV)

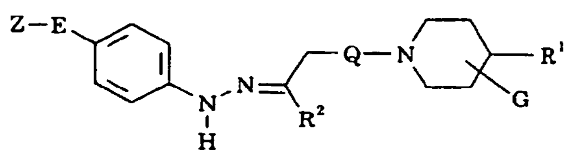
wherein Q, G, R^1 and R^2 are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The reaction between compounds III and IV, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating

the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives. Where the alkylene chain Q contains a hydroxy group, this group may condense with the carbonyl moiety in compound IV, whereby the carbonyl moiety is protected in the form of a cyclic hemiacetal.

The Fischer reaction between compounds III and IV may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula V:



(V)

wherein Z, E, Q, G, R^1 and R^2 are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The intermediates of formula IV, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VI, or a carbonyl-protected form thereof, with a compound of formula VII:

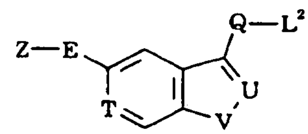
(VI) (VII)

wherein Q, G, R^1 and R^2 are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is suitably a halogen atom, e.g. chlorine or bromine.

Where L^1 represents a halogen atom, the reaction between compounds VI and VII is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in *N,N*-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

In an alternative procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VII as defined above with a compound of formula VIII:



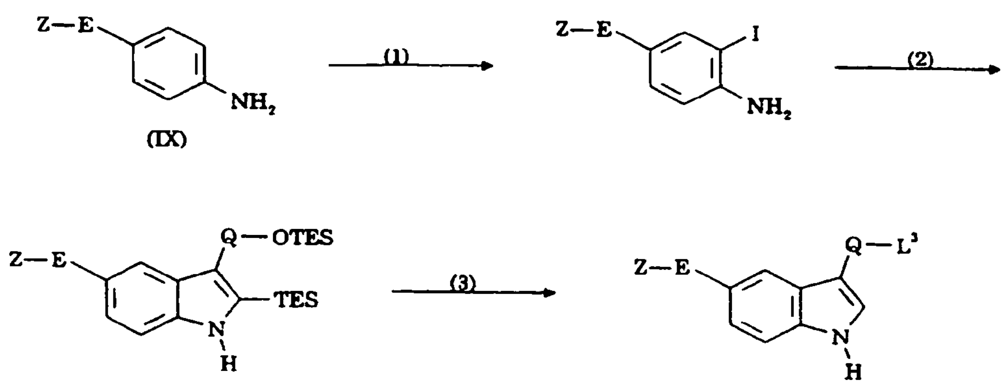
(VIII)

wherein Z, E, Q, T, U and V are as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

Where L^2 represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compounds VII and VIII is conveniently carried out in a suitable solvent such as 1,2-dimethoxyethane or isopropyl alcohol, typically in the presence of a base such as sodium carbonate or potassium carbonate, optionally with the addition of sodium iodide.

In one representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH and L^2 represents a mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, 113, 6689):



wherein Z, E and Q are as defined above, L^3 represents mesyloxy or tosyloxy, and TES is an abbreviation for triethylsilyl.

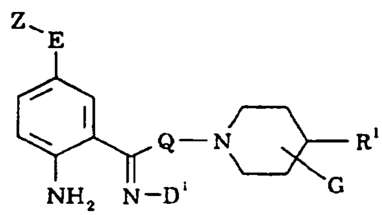
In Step 1 of the reaction scheme, the aniline derivative IX is treated with iodine monochloride, typically in methanol or acetonitrile, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TES-C≡C-Q-OTES, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethylformamide at an elevated temperature. This is followed in Step 3 by removal of the TES moiety, typically by treatment with hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in the presence of a base such as triethylamine or pyridine, typically in dichloromethane/acetonitrile.

In another representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH, Q represents a propylene chain and L^2 represents a mesyloxy or tosyloxy group may be prepared by reacting 3,4-dihydro-2*H*-pyran with a compound of formula III as defined above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds III and IV; followed by mesylation or tosylation of the 3-hydroxypropyl-indole

derivative thereby obtained, typically by treatment with mesyl chloride or tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2*H*-pyran is suitably brought about by stirring the pyran derivative with an acid addition salt of the hydrazine derivative III, typically the hydrochloride salt, in an inert solvent such as aqueous ethanol. The resulting hydrazide derivative can then be cyclised by treatment with a Lewis acid such as zinc chloride, in a solvent such as 1,2-dimethoxyethane, suitably at the reflux temperature of the solvent.

In a further procedure, the compounds according to the invention wherein U represents nitrogen and V represents N-R^3, corresponding to the indazole derivatives of formula IB as defined above, may be prepared by a process which comprises cyclising a compound of formula X:

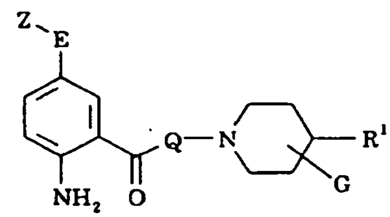


(X)

wherein Z, E, Q, G and R^1 are as defined above, and D^1 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C.

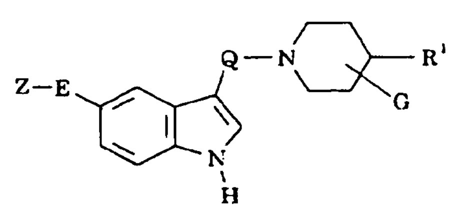
The readily displaceable group D^1 in the compounds of formula X suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^1 represents acetoxy, the desired compound of formula X may be conveniently prepared by treating a carbonyl compound of formula XI:



(XI)

wherein Z, E, Q, G and R^1 are as defined above; or a protected derivative thereof, preferably the N-formyl protected derivative; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivatives of the intermediates of formula XI may conveniently be prepared by ozonolysis of the corresponding indole derivative of formula XII:



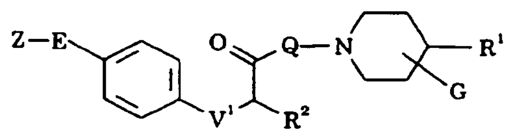
(XII)

wherein Z, E, Q, G and R^1 are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

In a still further procedure, the compounds according to the invention wherein T represents CH, U represents C-R^2 and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene

derivatives of formula IA wherein V is oxygen or sulphur respectively, may be prepared by a process which comprises cyclising a compound of formula XIII:

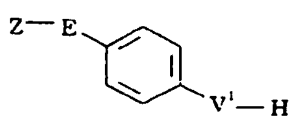


(XIII)

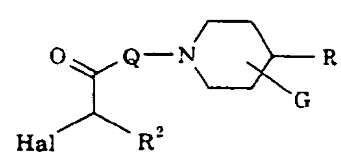
wherein Z, E, Q, G, R^1 and R^2 are as defined above, and V^1 represents oxygen or sulphur.

The cyclisation of compound XIII is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XIII may be prepared by reacting a compound of formula XIV with a compound of formula XV:



(XIV)



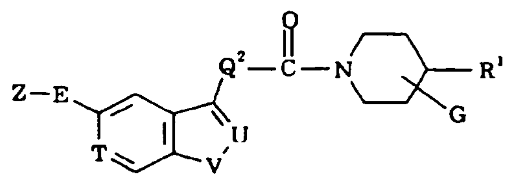
(XV)

wherein Z, E, Q, G, R^1, R^2 and V^1 are as defined above, and Hal represents a halogen atom.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XIV may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method is described in EP-A-0497512.

In a yet further procedure, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVI:

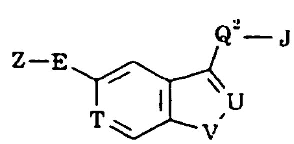


(XVI)

wherein Z, E, T, U, V, G and R^1 are as defined above, and $-Q^2-CH_2-$ corresponds to the moiety Q as defined above.

The reduction of compound XVI is conveniently effected by treating the appropriate compound with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

The compounds of formula XVI above may suitably be prepared by reacting the appropriate compound of formula VII as defined above with a compound of formula XVII:



(XVII)

wherein Z, E, T, U, V and Q^2 are as defined above, and J represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety J include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed

anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XVII above wherein J is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XVII wherein J is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula VII.

The hydrazine derivatives of formula III above may be prepared by methods analogous to those described in EP-A-0438230, EP-A-0497512, EP-A-0548813 and WO-A-91/18897, as also may the aniline derivatives of formula IX.

Where they are not commercially available, the starting materials of formula VI, VII, XV and XVII may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I initially obtained wherein the R^1 moiety is substituted by nitro or cyano may be converted by catalytic hydrogenation to the corresponding amino- or aminomethyl-substituted compound respectively. Additionally, a compound of formula I wherein the R^1 moiety is substituted by hydroxy, possibly obtained by lithium aluminium hydride reduction of a precursor

alkoxycarbonyl derivative, may be mesylated under standard conditions, and the mesyl group subsequently displaced by an amino moiety by treatment with the desired amine in a sealed tube at an elevated temperature. The amine derivative resulting from any of these procedures may then, for example, be N-acylated using the appropriate acyl halide, e.g. acetyl chloride; or aminocarbonylated, using potassium isocyanate, to the corresponding urea derivative; or converted to a 1,2,4-triazol-4-yl derivative using *N,N*-dimethylformamide azine; or reductively alkylated by treatment with the appropriate aldehyde or ketone in the presence of sodium cyanoborohydride. If desired, the amine derivative may also be carbamoylated by treatment with the requisite alkyl chloroformate. A compound of formula I initially obtained wherein the R^1 moiety is substituted by cyano may be converted, by treatment with sodium azide, to the corresponding tetrazole derivative, which in turn may be alkylated on the tetrazole ring by treatment with an alkyl halide under standard conditions. By way of additional illustration, a compound of formula I initially obtained wherein the R^1 moiety is substituted by an alkoxycarbonyl moiety may be saponified, by treatment with an alkali metal hydroxide, to the corresponding carboxy-substituted compound, which in turn may be converted to an amide derivative by treatment with the appropriate amine, advantageously in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole. Moreover, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in *N,N*-dimethylformamide.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be

prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1D_α} receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [^{35}S]-GTPγS binding to membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D_α}/5-HT_{1D_β} Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT_{1D_α} and 5-HT_{1D_β} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min.

The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended. in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, $CaCl_2$ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [^{3}H]-5-HT for saturation studies or 2-5 nM [^{3}H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μM) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-HT_{1D_α} receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT_{1D_α} receptor subtype of at least 10-fold relative to the 5-HT_{1D_β} subtype.

5-HT_{1D_α}/5-HT_{1D_β} Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT_{1D_α} and 5-HT_{1D_β} receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser. in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was

then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α-[^{33}P]-ATP to [^{33}P]-cyclic AMP. A 10 μl aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 μl, at 30°C, with or without forskolin (10 μM), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 μM GTP, 50 μM cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM $MgCl_2$, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 μCi α-[^{33}P]-ATP and 1 nCi [^{3}H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 μl SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT_{1D_α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype.

5-HT$_{1D\alpha}$/5-HT$_{1D\beta}$ GTPγS Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, **109**, 1120. CHO clonal cell lines expressing the human cloned 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, $MgCl_2$ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 μg protein/ml for the 5-HT$_{1D\alpha}$ receptor transfected cells and 40-50 μg protein/ml for the 5-HT$_{1D\beta}$ receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 μM for 5-HT$_{1D\alpha}$ receptor transfected cells, 30 μM for the 5-HT$_{1D\beta}$ receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min. [^{35}S]-GTPγS was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT$_{1D\alpha}$ receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess

at least a 10-fold selectivity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype.

INTERMEDIATE 1

3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propan-1-ol

1. 4-Aminoacetanilide

A solution of 4-nitroacetanilide (5.0g, 27.8mmol) in EtOH/EtOAc (160ml, 1:1), H_2O (15ml) and 5N HCl (5.6ml, 28.0mmol) was hydrogenated over 10% Pd-C (0.50g) at 50 psi for 0.25h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. The free base was generated by dissolving the product in H_2O, basifying with 2N NaOH and extracting into EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated to give the title-*aniline* (3.75g, 90%); δ_H (250MHz, $CDCl_3$/d_4-MeOH) 2.10 (3H, s, Me), 6.68 (2H, d, J=8.8Hz, Ar-H), 7.27 (2H, d, J=8.8Hz, Ar-H).

2. 4-(1,2,4-Triazol-4-yl)acetanilide

A mixture of the preceding aniline (3.52g, 23.4mmol), N,N-dimethylformamide azine (3.33g, 23.4mmol; *J. Chem. Soc. (C)*, 1967, 1664) and *p*-toluenesulphonic acid monohydrate (0.223g, 1.17mmol), in anhydrous toluene (100ml) was heated at reflux for 17h. The beige coloured precipitate was filtered off, washed with toluene and CH_2Cl_2, and dried under vacuum to give the desired triazole (4.29g, 91%). δ_H (250MHz, d_4-MeOH/d_6-DMSO) 2.14 (3H, s, CH_3), 7.60 (2H, d, J=8.8Hz, Ar-H), 7.78 (2H, d, J=8.8Hz, Ar-H), 8.96 (2H, s, Ar-H).

3. 4-(1,2,4-Triazol-4-yl)aniline

A solution of the preceding acetanilide (4.91g, 24.3mmol) in 5N HCl (100ml) was heated at 125°C for 1.5h. The mixture was cooled to 0°C, basified with concentrated aqueous NaOH solution and extracted with

CH_2Cl_2 (x5). The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1), to give the title-*aniline* (2.94g, 76%); δ_H (250MHz, $CDCl_3$) 3.80 (2H, s, NH_2), 6.71 (2H, d, J=8.8Hz, Ar-H), 7.08 (2H, d, J=8.8Hz, Ar-H), 8.36 (2H, s, Ar-H).

4. <u>4-(1,2,4-Triazol-4-yl)phenylhydrazine</u>

To a solution of the preceding aniline (1.60g, 9.99mmol) in concentrated HCl/H_2O (23ml and 3ml, respectively) was added, at -21°C, a solution of $NaNO_2$ (0.69g, 9.99mmol) in H_2O (8ml), at such a rate as to maintain the temperature below -10°C. The mixture was stirred for 0.3h and then filtered rapidly through a sinter, under vacuum. The filtrate was added to a cooled (-20°C) solution of $SnCl_2.2H_2O$ (9.02g, 40.0mmol) in concentrated HCl (17ml). The mixture was stirred at -20°C for 0.25h and then at room temperature for 1.25h. The resulting solid was filtered off, washed with Et_2O and dried under vacuum. The crude product was dissolved in H_2O, basified with concentrated aqueous NaOH and extracted with EtOAc (x5). The combined extracts were dried ($MgSO_4$) and evaporated to afford the *title-product* (0.95g, 54%); δ_H (250MHz, $CDCl_3$/d_4-MeOH) 3.98 (3H, br s, NH and NH_2), 6.97 (2H, d, J=12.0Hz, Ar-H), 7.25 (2H, d, J=12.0Hz, Ar-H), 8.48 (2H, s, Ar-H).

5. <u>3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propan-1-ol</u>

A solution of 4-(1,2,4-triazol-4-yl)phenylhydrazine (25g, 143mmol) in dioxan (250ml) was treated with dihydropyran (24g, 286mmol) followed by 1M hydrochloric acid (150ml) and heated at reflux for 18h. The reaction mixture was evaporated, treated with toluene the re-evaporated. Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother liquors were purified by column chromatography on silica using dichloromethane/methanol (9:1→4:1) as the eluant. The compound was recrystallised from acetonitrile to afford

the *title compound* as a colourless solid (10.24g, 30%); mp 205-207°C. (Found: C, 64.37; H, 5.76; N, 22.83. $C_{13}H_{14}N_4O$ requires: C, 64.45; H, 5.82; N, 23.13%.) δ_H (360MHz, DMSO-d_6) 1.81 (2H, q, J=7Hz, CH_2), 2.75 (2H, t, J=8Hz, CH_2), 3.46 (2H, dt, J_1=6, J_2=5Hz, CH_2), 4.43 (1H, t, J=5Hz, OH), 7.26 (1H, d, J=2Hz, Ar-H), 7.29 (1H, dd, J_1=9, J_2=2Hz, Ar-H), 7.47 (1H, d, J=9Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.05 (1H, br s, indole NH); m/z (CI) 243 (M^++1)

INTERMEDIATE 2

6-Aza-6-*tert*-butyloxycarbonyl-1-oxaspiro[2.5]octane

Dimethyl sulphoxide (100ml) was added dropwise to a stirred, cooled (10°C) mixture of sodium hydride (3.70g of a 55% oil dispersion, 0.0846mol) and trimethylsulphoxonium iodide (18.6g, 0.0846mol) under a nitrogen atmosphere. After addition the cooling bath was removed and the mixture stirred at room temperature for 30 minutes, then cooled to 5°C and was treated with a solution of *N-tert*-butyloxycarbonyl-4-piperidone (16.86g, 0.0846mol) in dimethylsulphoxide (50ml). The cooling bath was removed and the reaction mixture stirred at room temperature for 15 minutes, then at 50°C for 1 hour. The mixture was stirred whilst cooling to room temperature then quenched with water (40ml) and stirred for a further 10 minutes. The reaction mixture was poured into water (600ml) and extracted with toluene (4 x 300ml). The combined organics were washed with water (300ml), dried (sodium sulphate), then evaporated to give an oil which was eluted through a short silica column using ethyl acetate/n-hexane (1:1) to give a colourless solid (10.0g, 55%), mp 49-51°C. (Found: C, 61.88; H, 9.05; N, 6.42. $C_{11}H_{19}NO_3$ requires C, 61.95; H, 8.98; N, 6.57%). δ_H (360MHz, DMSO-d_6) 1.35-1.40 (2H, m, CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.60-1.67 (2H, m, CH_2), 2.65 (2H, s, CH_2O), 3.33-3.41 (2H, m, CH_2), 3.46-3.54 (2H, m, CH_2); m/z (ES) 214 (M^++1).

INTERMEDIATE 3

3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propan-1-ol

The *title compound* was obtained from 2-iodo-4-(1,2,4-triazol-1-ylmethyl)aniline and O,1-bis-triethylsilyl-1-pentyn-5-ol using the method described in *Tet. Letts.* **1994**, *35*, 6981-6984. mp 110°-112°C, δ_H (360MHz, DMSO-d_6) 1.79 (2H, qn, J=7Hz, $CH_2CH_2CH_2$), 2.70 (2H, t, J=7Hz, indole-CH_2), 3.47 (2H, q, J=7Hz, CH_2OH), 4.44 (1H, t, J=7Hz, OH), 5.44 (2H, s, CH_2-triazole), 7.04 (1H, dd, J=8 and 1Hz, Ar-H), 7.12 (1H, d, J=2Hz, Ar-H), 7.30 (1H, d, J=8Hz, Ar-H), 7.52 (1H, s, Ar-H), 7.94 (1H, s, triazole-H), 8.62 (1H, s, triazole-H), 10.80 (1H, s, indole-NH).

INTERMEDIATE 4

1-*tert*-Butyloxycarbonyl-4-ethynyl-4-fluoropiperidine

1. 1-*tert*-Butyloxycarbonyl-4-hydroxy-4-(2-trimethylsilylethynyl)-piperidine

To a cooled (-40°C) solution of trimethylsilylacetylene (34 ml, 241 mmol) in anhydrous tetrahydrofuran (400 ml) under an atmosphere of nitrogen was added slowly n-butyl lithium (96 ml of a 2.5M solution in hexanes, 241 mmol). After addition the mixture was stirred at -40°C for 1 hour then cooled to -78°C. To this mixture was added via a cannula a solution of 1-*tert*-butyloxycarbonyl-4-piperidone (40 g, 201 mmol) in anhydrous tetrahydrofuran (250 ml). After addition the mixture was stirred at -78°C for 1 hour, the cooling bath removed and the mixture stirred at room temperature for 72 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (300 ml), stirred for a further 10 minutes and poured into water (500 ml) and extracted with ethyl acetate (3 x 300 ml). The combined organic solutions were washed with water (500 ml), brine (300 ml), dried ($MgSO_4$) and evaporated to afford the *title compound* (55 g, 92%); mp 75°C; δ_H (250MHz, $CDCl_3$) 0.19

(9H, s), 1.48 (9H, s), 1.63-1.74 (2H, m), 1.80-1.92 (2H, m), 3.18-3.28 (2H, m), 3.71-3.84 (2H, m); m/z (ES) 298 (M^{+}+1).

2. 1-*tert*-Butyloxycarbonyl-4-hydroxy-4-(2-trimethylsilylethynyl)-piperidine-cobalt hexacarbonyl

To a solution of the product from the preceding step (55 g, 185 mmol) in diethyl ether (1000 ml) was added in a portionwise manner cobalt octacarbonyl (70 g, 203 mmol). After addition the mixture was stirred at room temperature for 4.5 hours then evaporated. The residue was purified by column chromatography (silica gel, hexane then diethyl ether-hexane 1:4) to give a red solid (80 g, 74%); δ_H (250MHz, $CDCl_3$) 0.32 (9H, s), 1.48 (9H, s), 1.75 (4H, m), 3.14 (2H, m), 4.03 (2H, m).

3. 1-*tert*-Butyloxycarbonyl-4-ethynyl-4-fluoropiperidine

To a cooled (-78°C) and stirred solution of diethylaminosulfur trifluoride (18.1 ml, 137 mmol) in anhydrous dichloromethane (250 ml) was added via a cannula a solution of the product from the preceding step (80 g, 137 mmol) in anhydrous dichloromethane (400 ml) over 20 minutes, under nitrogen. After a further 1 hour at -78°C, the mixture was warmed to room temperature and stirred for a further 2 hours. Diethyl ether (1000 ml) was added and the organic solution was washed with a mixture of water (600 ml) and saturated aqueous potassium carbonate (300 ml), followed by brine (1 x 300 ml), dried ($MgSO_4$) and concentrated. The residue was dissolved in acetone (750 ml) and ceric ammonium nitrate (226 g, 412 mmol) added in 5 g portions over 1 hour. After addition the mixture was stirred at room temperature for a further 3 hours then evaporated. The residue was treated with water (500 ml) and the products extracted with dichloromethane (3 x 300 ml). The combined organic solutions were washed with water (1 x 400 ml), brine (1 x 200 ml), dried ($MgSO_4$) and concentrated. The residue was dissolved in anhydrous tetrahydrofuran (200 ml) cooled at 0°C and tetrabutylammonium fluoride

(137 ml of a 1.1M solution in THF, 151 mmol) added. After addition the mixture was stirred at 0°C for 1 hour, then poured into water (500 ml) and products extracted with ethyl acetate (3 x 200 ml). The combined organic solutions were washed with water (1 x 400 ml), brine (1 x 200 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, diethyl ether-hexane 20:80) afforded 20 g (53%) of the required *title compound*, mp 45°C; δ_H (360MHz, $CDCl_3$) 1.46 (9H, s), 1.93-2.00 (4H, m), 2.70 (1H, d, *J*=5.0Hz), 3.45-3.60 (4H, m).

EXAMPLE 1

4-Benzyl-4-fluoro-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.1 Hydrogen Oxalate. 0.4 Hydrate

a) 1-*tert*-Butyloxycarbonyl-4-benzyl-4-hydroxypiperidine

A solution of 4-benzyl-4-hydroxypiperidine (14.5g, 75.8mmol) in dichloromethane (150ml) was treated portionwise with di-*tert*-butyl dicarbonate (16.55g, 75.8mmol) then stirred at ambient temperature for 4 hours. The solution was washed with 10% aqueous citric acid (50ml), dried (sodium sulphate), then evaporated to afford a gum (23.8g) which was purified by column chromatography on silica using ethyl acetate/petroleum ether (60-80) (1:1). The *product* was obtained (19.3g, 87%) as a pale yellow solid, mp 87-88°C; δ_H (360MHz, DMSO-d_6) 1.32-1.37 (13H, m, $(CH_3)_3C$ and $2xCH_2$), 2.67 (2H, s, CH_2Ph), 2.98-3.05 (2H, m, 2xCH), 3.63 (2H, d, J=12Hz, 2xCH), 4.37 (1H, s, OH), 7.15-7.27 (5H, m, C_6H_5); m/z (ES) 292 (M^++1).

b) 1-*tert*-Butyloxycarbonyl-4-benzyl-4-fluoropiperidine

To a cooled (-71°C) and stirred solution of diethylaminosulfur trifluoride (634μl, 4.80mmol) in anhydrous dichloromethane (15ml) was added dropwise, *via* cannula, a solution of 1-*tert*-butyloxycarbonyl-4-benzyl-4-hydroxypiperidine (700mg, 2.40mmol) in anhydrous

dichloromethane (15ml) over 20 minutes, under nitrogen. After a further 50 minutes at -75°C, the mixture was warmed to -10°C and stirred for a further 2 hours. Water (20ml) and saturated aqueous potassium carbonate (7ml) were added and products were extracted with diethyl ether (1x70ml). The organic solution was washed with brine (1x25ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, hexane-diethyl ether, 86:14) gave 190mg of 1-*tert*-butyloxycarbonyl-3,4-dehydro-4-benzylpiperidine and 360mg (51%) of the *title compound* as pale yellow oils; δ_H (360MHz, $CDCl_3$) 1.44 (9H, s), 1.46-1.78 (4H, m), 2.90 (2H, d, J=22Hz), 2.98-3.08 (2H, m), 3.86-3.94 (2H, m), 7.16-7.34 (5H, m); m/z (ES) 294 (M^+ +1).

c) <u>4-Benzyl-4-fluoropiperidine</u>

A solution of the product from the preceding step (360mg) in a mixture of trifluoroacetic acid and dichloromethane (1:2; 12ml) was allowed to stand at room temperature for 1 hour. Solvents were removed under vacuum and the residue was azeotroped with methanol (2x25ml). Water (10ml), 4N sodium hydroxide (5ml) and brine (15ml) were added and the product was extracted with ethyl acetate (2x50ml). The combined organic solutions were dried (Na_2SO_4) and concentrated to give 235mg (99%) of the *title compound* as a pale yellow oil which was used in the next step without further purification; δ_H (360MHz, $CDCl_3$) 1.50-1.78 (4H, m), 2.84-2.96 (6H, m), 7.16-7.32 (5H, m); m/z (ES) 194 (M^+ +1).

d) <u>4-Benzyl-4-fluoro-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.1 Hydrogen Oxalate. 0.4 Hydrate</u>

To a stirred suspension of Intermediate 1 (206mg, 0.85mmol) in anhydrous tetrahydrofuran (35ml) was added anhydrous triethylamine (237ml, 1.70mmol) followed by methanesulphonyl chloride (135μl, 1.70mmol) at room temperature, under nitrogen. After 1.5 hours of stirring, the mixture was diluted with ethyl acetate (100ml), washed with

brine (2x30ml), dried ($MgSO_4$) and concentrated (bath temperature 35°C). The remaining residue was dissolved in isopropanol (60ml), potassium carbonate (164mg, 1.19mmol) and a solution of 4-benzyl-4-fluoropiperidine (230mg, 1.19mmol) in isopropanol (10ml) were added, and the resulting mixture was refluxed for 18 hours, under nitrogen. The solvent was removed under vacuum, the residue was dissolved in water (50ml) and saturated aqueous potassium carbonate (4ml), and products were extracted with ethyl acetate (2x80ml). The combined extracts were washed with brine (1x35ml), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5) gave 164mg (46%) of the *title compound free base* as a white foam. The oxalate salt was prepared from ethanol-diethyl ether, mp 79-85°C. (Found: C, 57.15; H, 5.42; N, 11.24. $C_{25}H_{28}FN_5$ x 2.1($C_2H_2O_4$) x 0.4H_2O requires: C, 57.14; H, 5.42; N, 11.41%). δ_H (360MHz, DMSO-d_6) 1.84-2.10 (6H, m), 2.76 (2H, t, J=7.2Hz), 2.96-3.14 (6H, m), 3.32-3.42 (2H, m), 7.20-7.36 (7H, m), 7.51 (1H, d, J=8.5Hz), 7.80 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.18 (1H, s); m/z (ES) 418 (M^++1).

EXAMPLE 2

4-Fluoro-4-[2-(3-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate

a) 1-*tert*-Butyloxycarbonyl-4-[2-(3-fluorophenyl)ethyl]-4-hydroxypiperidine

To magnesium turnings (494mg), covered with anhydrous diethyl ether (3ml), was added one crystal of iodine followed by a small amount (10%) of a solution of 3-fluorobenzyl bromide (4.12g, 21.8mmol) in anhydrous diethyl ether (8ml). The mixture was warmed with a water bath (35°C) to initiate Grignard formation, then the remaining solution of 3-fluorobenzyl bromide was added dropwise over 30 minutes at the same temperature. Steady refluxing was observed, which ceased after 30

minutes. The resulting mixture was cooled to -30°C and a solution of Intermediate 2 (3.0g, 14.07mmol) in anhydrous diethyl ether (8ml) was added dropwise over 20 minutes. A large amount of gelatinous precipitate was formed making stirring difficult. The mixture was stirred at -10°C for a further 4 hours 15 minutes, then quenched with saturated ammonium chloride (100ml) and products were extracted with ethyl acetate (2x125ml). The combined organic solutions were washed with brine (50ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, hexane-diethyl ether, 50:50 to 30:70) afforded 935mg (20.5%) of the required *title compound*; δ_H (250MHz, $CDCl_3$) 1.47 (9H, s), 1.54-1.64 (4H, m), 1.72-1.82 (2H, m), 2.66-2.78 (2H, m), 3.12-3.26 (2H, m), 3.78-3.90 (2H, m), 6.82-7.00 (3H, m), 7.18-7.30 (1H, m); m/z (ES) 324 (M^+ +1).

b) 1-*tert*-Butyloxycarbonyl-4-fluoro-4-[2-(3-fluorophenyl)-ethyl]piperidine

To a cooled (-72°C) and stirred solution of diethylaminosulfur trifluoride (760μl, 5.75mmol) in anhydrous dichloromethane (10ml) was added dropwise, *via* cannula, a solution of the preceding alcohol (930mg, 2.87mmol) in anhydrous dichloromethane (15ml) over 40 minutes, under nitrogen. After a further 50 minutes at -75°C, the mixture was warmed to -5°C and stirred for 2 hours. Diethyl ether (100ml) was added and the organic solution was washed with water-saturated aqueous potassium carbonate (2:1, 30ml), brine (35ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, hexane-diethyl ether, 86:14) gave 500mg of the *title compound*, impurified with 1-*tert*-butyloxycarbonyl-3,4-dehydro-4-[2-(3-fluorophenyl)ethyl]piperidine (*ca* 3:1). This was dissolved in dichloromethane (25ml), m-chloroperoxy-benzoic acid (80-85%; 400mg) was added, and the mixture was allowed to stand at room temperature for 12 hours. Diethyl ether (150ml) was added and the solution was washed with 2N sodium hydroxide (25ml), 2N

sodium hydroxide - 10% aqueous sodium thiosulphite (1:1, 30ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, hexane-diethyl ether, 86:14) afforded 305mg (33%) of the *title compound* as a colourless thick oil which solidified on standing; δ_H (250MHz, $CDCl_3$) 1.47 (9H, s), 1.50-2.00 (6H, m), 2.68-2.78 (2H, m), 3.02-3.16 (2H, m), 3.90-4.00 (2H, m), 6.84-7.00 (3H, m), 7.18-7.30 (1H, m); m/z (ES) 326 (M^++1).

c) <u>4-Fluoro-4-[2-(3-fluorophenyl)ethyl]piperidine</u>

The *title compound* was prepared from the product of the preceding step following a similar method to that described for Example 1, step c. δ_H (250MHz, $CDCl_3$-CD_3OD) 1.50-1.78 (2H, m), 1.82-2.00 (4H, m), 2.66-2.80 (2H, m), 2.88-3.00 (4H, m), 6.82-7.02 (3H, m), 7.18-7.30 (1H, m); m/z (ES) 226 (M^++1).

d) <u>4-Fluoro-4-[2-(3-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate</u>

The title *compound free base* was prepared from Intermediate 1 and the product from the preceding step following a silimar method to that described for Example 1, step d. The oxalate salt was prepared from ethanol-diethyl ether, mp 70-80°C. (Found: C, 57.06; H, 5.29; N, 11.17. $C_{26}H_{29}F_2N_5$ x $2.0C_2H_2O_4$ requires: C, 57.23; H, 5.28; N, 11.12%). δ_H (360MHz, DMSO-d_6) 1.86-2.14 (8H, m), 2.65-2.82 (4H, m), 3.00-3.20 (4H, m), 3.30-3.46 (2H, m), 6.96-7.12 (3H, m), 7.26-7.36 (3H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, s), 9.02 (2H, s), 11.18 (1H, s); m/z (ES) 450 (M^++1).

Examples 3 and 4 were prepared from 1-*tert*-butyloxycarbonyl-4-(3-fluorobenzyl)-4-hydroxypiperidine and 1-*tert*-butyloxycarbonyl-4-(2-fluorobenzyl)-4-hydroxypiperidine (see Example 7, step a) following a similar procedure to that described for Example 1 (steps b, c and d).

EXAMPLE 3

4-Fluoro-4-(3-fluorobenzyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 1.5 Hydrogen Oxalate. 0.5 Etherate

The oxalate salt was prepared from ethanol-diethyl ether, mp 80-83°C. (Found: C, 52.22; H, 5.00; N, 9.30. $C_{25}H_{27}F_2N_5$ x $1.5C_2H_2O_4$ x $0.5C_4H_{10}O$ requires: C, 52.03; H, 5.03; N, 9.19%). δ_H (360MHz, 9:1 $CDCl_3$-DMSO-d_6) 1.86-1.97 (2H, m), 2.04-2.56 (4H, m), 2.87-2.98 (6H, m), 3.02-3.09 (2H, m), 3.40-3.50 (2H, m), 6.89-7.00 (3H, m), 7.13 (1H, dd, J=8 and 2 Hz), 7.22-7.33 (2H, m), 7.50 (1H, d, J=8Hz), 7.55 (1H, d, J=2Hz), 8.56 (2H, s) and 10.30 (1H, s); m/z (ES) 436 (M^++1).

EXAMPLE 4

4-Fluoro-4-(2-fluorobenzyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 1.0 Hydrogen Oxalate. 0.6 Hydrate

The oxalate salt was prepared from ethanol-diethyl ether, mp 84-89°C. (Found: C, 55.75; H, 5.47; N, 11.22. $C_{25}H_{27}F_2N_5$ x $1.0C_2H_2O_4$ x $0.6H_2O$ requires: C, 55.61; H, 5.18; N, 11.18%). δ_H (360MHz, 9:1 $CDCl_3$-DMSO-d_6+CF_3CO_2H) 1.92-2.00 (2H, m), 2.25-2.56 (4H, m), 2.84-3.12 (8H, m), 3.40-3.50 (2H, m), 7.04-7.30 (6H, m), 7.51 (1H, d, J=8Hz), 7.66 (1H, s) and 8.80 (2H, s); m/z (ES) 436 (M^++1).

EXAMPLE 5

4-Benzyl-4-methoxy-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. Hydrogen Oxalate.

a) 1-*tert*-Butyloxycarbonyl-4-benzyl-4-methoxypiperidine

1-*tert*-Butyloxycarbonyl-4-benzyl-4-hydroxypiperidine (Example 1, step a) (2.0g, 6.87mmol) was added to a stirred mixture of finely powdered potassium hydroxide (1.54g, 27.5mmol) in dimethyl sulphoxide (20ml). After addition, the mixture was treated with iodomethane (0.85ml, 13.7mmol) then stirred at ambient temperature for 1 hour, poured into

water (100ml) and extracted with ethyl acetate (2x30ml). The combined organics were washed with water (2x30ml), dried (sodium sulphate) then evaporated to afford a gum (2.22g) which was purified by column chromatography on silica using ethyl acetate/n-hexane (1:1). The *title compound* was obtained as a viscous colourless gum (1.23g, 59%); δ_H (250MHz, $CDCl_3$) 1.36-1.50 (2H, m, 2xCH), 1.43 (9H, s, $(CH_3)_3C$), 1.62-1.77 (2H, m, 2xCH), 2.77 (2H, s, CH_2Ph), 2.95-3.06 (2H, m, 2xCH), 3.34 (3H, s, OCH_3), 3.70-3.90 (2H, m, 2xCH), 7.11-7.32 (5H, m, C_6H_5); m/z (ES) 306 (M^+ +1).

b) 4-Benzyl-4-methoxypiperidine

The product from the preceding step (1.22g, 4.0mmol) and trifluoroacetic acid (3.1ml, 40mmol) in dichloromethane (20ml) were stirred at ambient temperature for 24 hours. The solvent was evaporated and the residue partitioned between dichloromethane (30ml) and saturated aqueous potassium carbonate solution (30ml). The organic layer was separated then the aqueous re-extracted with dichloromethane (30ml). The combined organics were dried (potassium carbonate) then evaporated to give a yellow gum (0.90g) which was purified by column chromatography on silica using dichloromethane/methanol/ammonia (9:1:0.1). The *title compound* was obtained as a colourless viscous gum (0.80g, 98%); δ_H (250MHz, $CDCl_3$) 1.43-1.51 (2H, m, 2xCH), 1.68 (2H, d, J=12Hz, 2xCH), 2.77 (2H, s, CH_2Ph), 2.78-2.92 (4H, m, $2xCH_2$), 3.33 (3H, s, OCH_3), 7.14-7.30 (5H, m, C_6H_5); m/z (ES) 206 (M^+ +1).

c) 4-Benzyl-4-methoxy-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. Hydrogen Oxalate

The *title compound free base* (135mg, 29%) was obtained from the mesylate of 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and 4-benzyl-4-methoxypiperidine as described previously (Example 1, step d). The hydrogen oxalate salt had mp 110°-115°C. (Found: C, 61.99; H, 6.49; N,

12.09. $C_{26}H_{31}N_5O$ x $1.47C_2H_2O_4$ requires; C, 61.86; H, 6.09; N, 12.46%).δ_H (360MHz, DMSO-d_6) 1.65-1.74 (2H, m, 2xCH), 1.82 (2H, d, J=12Hz, 2xCH, 1.98-2.06 (1H, m, $CH_2CH_2CH_2$), 2.76 (2H, t, J=7Hz, indole-CH_2), 2.82 (2H, s, CH_2Ph), 2.82-3.00 (2H, m, 2xCH), 3.02-3.10 (2H,m, CH_2N), 3.20-3.32 (2H, m, 2xCH), 3.27 (3H, s, OCH_3), 7.18-7.34 (7H, m, indole-H, C_6H_5, Ar-H), 7.50 (1H, d, J=8Hz, Ar-H), 7.79 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.18 (1H, s, indole-NH), m/z (ES) 430 (M^++1).

EXAMPLE 6

4-Benzyl-4-methoxy-1-(3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]propyl)piperidine Hydrogen Oxalate

A stirred, cooled (-5°C) solution of 3-(5-[1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)propan-1-ol (260mg, 1mmol) in anhydrous tetrahydrofuran (20ml), under a nitrogen atmosphere, was treated with triethylamine (0.17ml, 1.2mmol) and methanesulphonyl chloride (0.10ml, 1.2mmol). After 45 minutes the reaction mixture was filtered, then washed through the filter pad with tetrahydrofuran (10ml). The resulting mesylate solution was treated with potssium carbonate (263mg, 1.9mmol), sodium iodide (285mg, 1.9mmol) and a solution of 4-benzyl-4-methoxypiperidine (400mg, 1.9mmol) in tetrahydrofuran (10ml). The reaction mixture was stirred whilst heating at 50°C for 24 hours. The solvent was evaporated, the residue partitioned between dichloromethane (40ml) and water (20ml). The organic layer was separated and the aqueous re-extracted with dichloromethane (40ml). The combined organics were extracted with aqueous citric acid (1g in 20ml), the aqueous was basified to pH=12 with 40% aqueous soldium hydroxide then extracted with dichloromethane (3x30ml). The organic extracts were combined, dried (potassium carbonate) then evaporated. The residue was purified by column chromatography on silica using dichloromethane/methanol/ammonia (9:1:0.1) to afford the *title compound free base* as a glass (332mg, 75%). The hydrogen oxalate salt has mp 84°-87°C. (Found: C, 60.81; H, 6.34; N,

11.68. $C_{27}H_{33}N_5O$. $1.75C_2H_2O_4$ requires C, 60.94; H, 6.12; N, 11.65%). δ_H (360MHz, DMSO-d_6) 1.65-1.78 (2H, m, 2xCH), 1.82 (2H, d, J=12Hz, 2xCH), 1.94-2.04 (2H, m, $CH_2CH_2CH_2$), 2.71 (2H, t, J=7Hz, indole-CH_2), 2.82 (2H, s, CH_2Ph), 2.82-3.00 (2H, m, 2xCH), 3.02-3.12 (2H, m, CH_2N), 3.22-3.32 (2H, m, 2xCH), 3.28 (3H, s, OCH_3), 5.43 (2H, s, CH_2-triazole), 7.05 (1H, d, J=7Hz, Ar-H), 7.18-7.34 (7H, m, C_6H_5, indole-H, Ar-H), 7.52 (1H, s, Ar-H), 7.94 (1H, s, triazole-H), 8.60 (1H, s, triazole-H), 10.92 (1H, s, indole-NH); m/z (ES) 444 (M^+ +1).

EXAMPLE 7

4-(2-Fluorobenzyl)-4-methoxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine Hydrogen Oxalate

a) 1-*tert*-Butyloxycarbonyl-4-(2-fluorobenzyl)-4-hydroxypiperidine

1-Benzyl-4-piperidone (10g, 53mmol) in diethyl ether (80ml) was added dropwise to a cooled (-4°C), stirred mixture of 2-fluorobenzyl magnesium bromide (prepared from magnesium and 2-fluorobenzyl bromide (9.56ml, 80mmol) in diethyl ether (65ml)) under an atmosphere of nitrogen. The reaction mixture was stirred whilst warming to room temperature (30 minutes) then at room temperature for 20 minutes. The reaction mixture was quenched with 2M hydrochloric acid (100ml). The aqueous was separated and washed with diethyl ether (100ml). The aqueous was basified with 2M sodium hydroxide solution then exhaustively extracted with dichloromethane. The combined organics were dried (sodium sulphate) then evaporated to give crude 1-benzyl-4-(2-fluorobenzyl)-4-hydroxypiperidine as a gum (9.0g). This crude product in methanol (100ml) was treated with formic acid (6ml), ammonium formate (9.5g, 0.15mol) and 10% palladium on carbon (900mg). The mixture was stirred whilst heating at reflux for 4 hours, cooled, filtered then evaporated to afford 4-(2-fluorobenzyl)-4-hydroxypiperidine as a gum (3.4g); m/z (ES) 210 (M^++1). This amine (3.35g, 16mmol) in

dichloromethane (75ml) was treated with di-t-butyldicarbonate (3.5g, 16mmol) and stirred at ambient temperature for 18 hours, washed with aqueous 10% citric acid, dried (potassium carbonate), evaporated to give a gum which was purified by column chromatography on silica using ethyl acetate/n-hexane (1:1) to afford the *title compound* as a colourless, viscous gum (3.62g, 73%). δ_H (360MHz, $CDCl_3$) 1.46 (9H, s, $(CH_3)_3C$), 1.48 (2H, d, J=13Hz, 2xCH), 1.63 (2H, ddd, J_1=5, J_2=13, J_3=17Hz, 2xCH), 2.82 (2H, d, J=1Hz, CH_2Ph), 3.11 (2H, ddd, J_1=3, J_2=J_3=13Hz, 2xCH), 3.84 (2H, d, J=13Hz, 2xCH), 7.02-7.27 (4H, m, C_6H_4); m/z (ES) 310 (M^++1).

b) 1-*tert*-Butyloxycarbonyl-4-(2-fluorobenzyl)-4-methoxypiperidine

The title compound was obtained (320mg, 31%) from the product of the preceding step as described for Example 5 (step a); δ_H (360MHz, DMSO-d_6) 1.30-1.34 (2H, m, 2xCH), 1.36 (9H, s), $(CH_3)_3C$), 1.60-1.64 (2H, m, 2xCH), 2.80 (2H, s, CH_2Ph), 2.82-2.98 (2H, m, 2xCH), 3.25 (3H, s, OCH_3), 3.65-3.68 (2H, m, 2xCH), 7.10-7.28 (4H, m, C_6H_4); m/z (ES) 324 (M^+ +1).

c) 4-(2-Fluorobenzyl)-4-methoxypiperidine

The *title compound* was obtained (181mg, 82%) from the product of the preceding step as described for Example 5 (step b); δ_H (250MHz, DMSO-d_6) 1.37-1.49 (2H, m, 2xCH), 1.64-1.68 (2H, m, 2xCH), 2.65-2.75 (4H, m, $2xCH_2$), 2.87 (2H, s, CH_2Ph), 3.34 (3H, s, OCH_3), 7.21-7.43 (4H, m, C_6H_4); m/z (ES) 224 (M^++1).

d) 4-(2-Fluorobenzyl)-4-methoxy-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine Hydrogen Oxalate

The *title compound free base* was obtained (105mg, 33%) from the mesylate of 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and 4-(2-fluorobenzyl)-4-methoxypiperidine as described previously. The hydrogen oxalate salt had mp 110°-115°C. (Found: C, 56.94; H, 5.80; N, 11.04.

$C_{26}H_{30}FN_5O$. $2.1C_2H_2O_4$ requires: C, 56.98; H, 5.42; N, 11.00%). δ_H (360MHz, DMSO-d_6) 1.64-1.78 (2H, m, 2xCH), 1.80-188 (2H, m, 2xCH), 1.96-2.04 (2H, m, $CH_2CH_2CH_2$), 2.70-2.78 (2H, m, indole-CH_2), 2.84 (2H, s, *CH*Ph), 2.90-2.98 (2H, m, 2xCH), 3.02-3.10 (2H, m, CH_2N), 3.26 (3H, s, OCH_3), 3.25-3.32 (2H, m, 2xCH), 7.13-7.33 (6H, m, C_6H_4, Ar-H, indole-H), 7.49 (1H, d, J=8Hz, Ar-H), 7.89 (1H, s, Ar-H), 9.00 (2H, s, 2 x triazole-H), 11.18 (1H, s, indole-NH); m/z (ES) 448 (M^++1).

EXAMPLE 8

4-(3-Fluorobenzyl)-4-methoxy-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine Hydrogen Oxalate

The *title compound free base* was obtained (85mg, 44%) from the mesylate of 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and 4-(3-fluorobenzyl)-4-methoxypiperidine as described previously. The hydrogen oxalate salt had mp > 105°C. (Found: C, 57.81; H, 5.95; N, 11.05%. $C_{26}H_{30}FN_5O$. $1.85C_2H_2O_4$ requires: C, 58.09; H, 5.53; N, 11.40%); m/z (ES) 448 (M^++1).

EXAMPLE 9

4-(4-Fluorobenzyl)-4-methoxy-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine Hydrogen Oxalate

The *title compound free base* was obtained (50mg, 20%) from the mesylate of 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and 4-(4-fluorobenzyl)-4-methoxypiperidine as described previously. The hydrogen oxalate salt had mp > 95°C (dec.). (Found: C, 58.77; H, 5.89; N, 11.53. $C_{26}H_{30}FN_5O$. $1.75C_2H_2O_4$ requires: C, 58.55; H, 5.58; N, 11.57%); m/z (ES) 448 (M^++1).

EXAMPLE 10

4-Fluoro-4-[2-(trifluoromethyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate. 0.4 Etherate. 0.25 Hydrate.

a) 1-*tert*-Butyloxycarbonyl-4-[2-(trifluoromethyl)benzyl]-4-hydroxypiperidine

2-Bromobenzotrifluoride (0.70 ml, 5.1 mmol) was added dropwise at -78°C to a stirred solution of *tert*-butyllithium (1.7 M in pentane, 6.0 ml) in anhydrous diethyl ether (25 ml) under nitrogen. After 30 minutes, a solution of Intermediate 2 (1.0 g, 4.69 mmol) was added. The white suspension was stirred at -78°C for 1.5 hours, then warmed slowly to room temperature and stirred for a further 18 hours. The mixture was diluted with saturated aqueous ammonium chloride (100 ml) and extracted with diethyl ether (2 x 50 ml). The extracts were dried ($MgSO_4$), filtered and concentrated. Flash column chromatography on silica, eluting with 30% then 50% ethyl acetate-hexane, gave the *product* (1.44 g, 86%) as a pale yellow glass; δ_H (360 MHz, $CDCl_3$) 1.45 (9 H, s), 1.49 (2 H, dd, J=13 and 2), 1.65 (2 H, ddd, J=13, 13 and 5), 2.99 (2 H, s), 3.05 (2 H, ddd, J=13, 13 and 3), 3.90 (2 H, broad d, J=13), 7.35 (1 H, dd, J=7 and 7), 7.47-7.55 (2 H, m) and 7.67 (1 H, d, J=8); m/z (ES) 360 (M^++1).

b) 1-*tert*-Butyloxycarbonyl-4-[2-(trifluoromethyl)benzyl]-4-fluoropiperidine

The *title compound* (0.70 g, 49%) was prepared from the product of the preceding step (1.43 g, 3.98 mmol) following a similar method to that described for Example 2, step b. δ_H (360 MHz, $CDCl_3$) 1.46 (9 H, s), 1.55-1.68 (4 H, m), 2.92-3.03 (2 H, m), 3.13 (2 H, d, J=24), 3.88-4.04 (2 H, m), 7.35 (1 H, dd, J=8 and 8), 7.49 (1 H, d, J=8 and 8), 7.57 (1 H, d, J=8) and 7.65 (1 H, d, J=8); m/z (ES) 384 [M^++23 (Na)].

c) 4-[2-(Trifluoromethyl)benzyl]-4-fluoropiperidine

The *title compound* (0.454 g, 92%) was prepared from the product of the preceding step (0.687 g, 1.90 mmol) following a similar method to that described for Example 1, step c. δ_H (250 MHz, $CDCl_3$) 1.50-1.75 (4 H, m)2.81-2.94 (4 H, m), 3.13 (2 H, d, J=24), 7.34 (1 H, dd, J=8 and 8), 7.49 (1 H, dd, J=8 and 8), 7.58 (1 H, d, J=8) and 7.65 (1 H, d, J=8); m/z (ES) 262 (M^++1).

d) 4-Fluoro-4-[2-(trifluoromethyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol- 3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate. 0.4 Etherate. 0.25 Hydrate.

The *title compound free base* (0.133 g, 29%) was prepared from Intermediate 1 and the product of the preceding step following a similar method to that described for Example1, step d. The oxalate salt was prepared from ethanol-diethyl ether, m.p. 88-91 °C. (Found: C, 54.24; H, 4.90; N, 9.76. $C_{26}H_{27}N_5F_4$ x $2.0C_2H_2O_4$ x $0.4C_4H_{10}O$ x $0.25H_2O$ requires C, 54.24; H, 5.11; N, 10.01%.) δ_H (360 MHz, 9:1 $CDCl_3$+d_6-DMSO) 1.58-1.66 (2 H, m), 1.90-2.10 (4 H, m), 2.54-2.60 (2 H, m), 2.65-2.78 (2 H, m), 2.80-2.87 (2 H, m), 2.91 (2 H, d, J=24), 3.18-3.24 (2 H, m), 6.86 (1 H, dd. J=9 and 1), 6.92 (1 H, s), 7.13 (1 H, dd, J=8 and 8), 7.21-7.27 (4 H. m), 7.38 (1 H, d, J=8), 8.30 (2 H, s) and 10.25 (1 H, s); m/z (ES) 486 (M^++1).

EXAMPLE 11

4-Fluoro-4-[2-(N, N-dimethylaminosulfonyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate. 0.2 Etherate. 0.5 Hydrate.

Example 11 was prepared from N,N-dimethylbenzenesulfonamide following a similar procedure to that described for Example 10 (steps a, b, c and d).

The oxalate salt was prepared from ethanol-diethyl ether, m.p. 94-98 °C. (Found: C, 52.49; H, 5.41; N, 11.48. $C_{27}H_{33}N_6SO_2F$ x $2.0C_2H_2O_4$ x

$0.2C_4H_{10}O$ x $0.5H_2O$ requires C, 52.43; H, 5.53; N, 11.54%.) δ_H (360 MHz, d_6-DMSO) 1.76-1.86 (2 H, m), 1.90-2.15 (4 H, m), 2.68 (6 H, s), 2.72-2.80 (2 H, m), 2.92-3.05 (2 H, m), 3.06-3.14 (2 H, m), 3.36-3.44 (2 H, m), 3.46 (2 H, d, J=25), 7.31-7.33 (2 H, m), 7.49-7.56 (3 H, m), 7.67 (1 H, dd, J=7), 7.79-7.81 (2 H, m), 9.00 (2 H, s) and 11.18 (1 H, s);m/z (ES) 525 (M^++1).

EXAMPLE 12

4-Fluoro-4-(2-phenylpropyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate. 0.15 Etherate. 0.05 Hydrate.

a) 1-*tert*-Butyloxycarbonyl-4-[(2-phenyl)allyl]-4-hydroxypiperidine

A solution of *tert*-butyllithium in pentane (1.7 M, 11 ml) was added dropwise at -78 °C to a stirred solution of a-bromostyrene (2.3 ml, 17.7 mmol) in anhydrous THF (80 ml) under nitrogen. After 20 minutes, a solution of Intermediate 2 (2.0 g, 9.38 mmol) in anhydrous THF (6 ml) was added. The black solution was warmed slowly to room temperature over 7 hours. The mixture was diluted with saturated aqueous ammonium chloride (200 ml) and extracted with ethyl acetate (100 ml). The extract was washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated. Flash column chromatography on silica, eluting with 20% then 60% ethyl acetate-hexane, gave the *title compound* (1.67 g, 56%) as a yellow oil. δ_H (360 MHz, $CDCl_3$) 1.39-1.47 (13 H, m), 1.57 (1 H, s), 2.74 (2 H, s), 2.98-3.10 (2 H, m), 3.70-4.02 (2 H, m) and 7.26-7.42 (5 H, m); m/z (ES) 318 (M^++1).

b) 1-*tert*-Butyloxycarbonyl-4-(2-phenylpropyl)-4-hydroxypiperidine

A solution of 1-*tert*-butyloxycarbonyl-4-[(2-phenyl)allyl]-4-hydroxypiperidine (1.67 g, 5.26 mmol) in ethyl acetate (25 ml) was hydrogenated over 1% palladium on activated carbon (0.8 g) at room temperature and 1 atm pressure of hydrogen for 1.5 hours. The mixture was filtered and the filtrate was concentrated to yield the *title compound* (1.47 g, 87%) as a pale yellow glass. δ_H (250 MHz, $CDCl_3$) 1.27 (3 H, d,

J=7), 1.36-1.60 (13 H, m), 1.73 (1 H, dd, J=15 and 4), 2.01 (1 H, dd, J=15 and 10), 2.98-3.06 (3 H, m), 3.60-3.88 (2 H, m) and 7.16-7.36 (5 H, m); m/z (ES) 320 (M^{+}+1).

c) 1-*tert*-Butyloxycarbonyl-4-(2-phenylpropyl)-4-fluoropiperidine

The *title compound* (0.651 g, 44%) was prepared from the product of the preceding step (1.47 g, 4.60 mmol) following a similar method to that described for Example 2, step b. δ_H (250 MHz, $CDCl_3$) 1.28 (3 H, d, J=7), 1.43 (9 H, s), 1.47-2.11 (6 H, m), 2.93-3.07 (3 H, m), 3.76-3.86 (2 H, m) and 7.15-7.33 (5 H, m); m/z (ES) 322 (M^{+}+1).

d) 4-(2-Phenylpropyl)-4-fluoropiperidine

The *title compound* (0.374 g, 85%) was prepared from the product of the preceding step (0.640 g, 1.99 mmol) following a similar method to that described for Example 1, step c. δ_H (360 MHz, $CDCl_3$) 1.28 (3 H, d, J=7), 1.35-1.60 (2 H, m), 1.70-1.79 (2 H, m), 1.83-2.09 (2 H, m), 2.79-2.93 (4 H, m), 3.03 (1 H, qt, J=7 and 7), 7.15-7.22 (3 H, m) and 7.26-7.31 (2 H, m); m/z (ES) 222 (M^{+}+1).

e) 4-Fluoro-4-(2-phenylpropyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 2.0 Hydrogen Oxalate. 0.15 Etherate. 0.05 Hydrate.

The *title compound free base* (0.119 g, 32%) was prepared from Intermediate 1 and the product of the preceding step following a similar method to that described for Example1, step d. The oxalate salt was prepared from ethanol-diethyl ether, m.p. 87-91 °C. (Found: C, 59.24; H, 5.95; N, 11.28. $C_{27}H_{32}N_5F$ x $2.0C_2H_2O_4$ x $0.15C_4H_{10}O$ x $0.05H_2O$ requires C, 59.52; H, 5.94; N, 10.98%.) δ_H (360 MHz, d_6-DMSO) 1.21 (3 H, d, J=7), 1.60-2.10 (10 H, m), 2.75 (2 H, t, J=8), 2.90-3.12 (4 H, m), 3.26-3.28 (1 H, m), 7.16-7.20 (1 H, m), 7.24-7.35 (6 H, m), 7.50 (1 H, d, J=9), 7.79 (1 H, s), 9.01 (2 H, s) and 11.17 (1 H, s); m/z (ES) 446 (M^{+}+1).

EXAMPLE 13

4-Fluoro-4-[3-fluoro-(2-phenyl)propyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine.

a) 3-(1-*tert*-Butyloxycarbonyl-4-hydroxypiperidin-4-yl)-2-phenyl-propionic acid methyl ester

A solution of lithium hexamethyldisilylamide (1 M, 22 ml) in THF was diluted with dry THF (40 ml) and stirred at -70 °C under nitrogen. Methyl 2-phenylacetate (3.00 ml, 20.9 mmmol) was added dropwise and the orange solution was stirred for 30 minutes. A solution of Intermediate 2 (4.26 g, 20 mmol) in dry THF (12 ml) was added, followed by dropwise addition of boron trifluoride etherate (2.5 ml, 20.3 mmol). The mixture was stirred at -70 °C for 1.5 hours, then warmed slowly to room temperature and stirred for a further 17 hours. The yellow solution was diluted with saturated aqueous ammonium chloride (100 ml) and extracted with ethyl acetate (3 x 50 ml). The extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated. Flash column chromatography on silica, eluting with 40% ethl acetate-hexane, gave the *title compound* (4.64 g, 64%) as a viscous, colourless oil. δ_H (360 MHz, $CDCl_3$) 1.45 (9 H, s), 1.47-1.69 (4 H, m), 1.78 (2 H, dd, J=15 and 4), 2.53 (1 H, dd, J=15 and 10), 3.06-3.18 (2 H, m), 3.66 (3 H, s), 3.72-3.85 (2 H, m), 3.86 (2 H, dd, J=10 and 4) and 7.24-7.34 (5 H, m); m/z (ES) 364 (M^++1).

b) 1-*tert*-Butyloxycarbonyl-4-hydroxy-4-[3-hydroxy-(2-phenyl)propyl]piperidine.

A solution of the product of the previous step (3.50 g, 9.63 mmol) in dry THF (50 ml) was added dropwise *via cannula* to a stirred solution of lithium aluminium hydride (1 M in THF, 20 ml) in dry THF (30 ml) at under nitrogen, cooling the mixture in an ice-bath as necessary to control the mild exotherm. After stirring for 1.5 hours at room temperature the soultion was cooled to 0°C and aqueous sodium hydroxide (1 M, 5 ml) was

added dropwise. The resulting gel was diluted with water (50 ml0 and acidified to pH 3-4 with aqueous citric acid (1 M, 50 ml), then extracted with ethyl acetate (3 x 100 ml). The extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated. Dry flash chromatography, eluting with 50% then 66% ethyl acetate-hexane, then ethyl acetate, gave the *title compound* (2.77 g, 86%) as a colourless glass. δ_H (360 MHz, $CDCl_3$) 1.44 (9 H, s), 1.45-1.69 (4 H, m), 1.96 (2 H, d, J=9), 3.06-3.21 (3 H, m), 3.66-3.81 (4 H, m) and 7.19-7.37 (5 H, m); m/z (ES) 336 (M^{+}+1).

c) 1-*tert*-Butyloxycarbonyl-4-hydroxy-4-[3-tosyloxy-(2-phenyl)propyl]piperidine.

A solution of the product of the previous step (1.67 g, 4.98 mmol) in dry pyridine (40 ml) under nitrogen was stirred at 0°C and tosyl chloride (2.37 g, 12.5 mmol) was added in one portion. After stirring for 19 hours at 0°C the yellow soultion was poured onto crushed ice (150 ml), acidified to pH 5 with aqueous citric acid (1 M, 250 ml) and extracted with diethyl ether (4 x 100 ml). The extracts were washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated. The resulting solid was washed with 5% ethyl acetate-hexane (100 ml) and dried *in vacuo* to yield the *title compound* (1.86 g, 76%) as very pale pink granules. δ_H (360 MHz, $CDCl_3$) 1.25-1.50 (4 H, m), 1.43 (9 H, s), 1.50-1.60 1 H, m), 1.91 (2 H, d, J=6), 2.43 (3 H, s), 2.96-3.16 (2 H, m), 3.21-3.28 (1 H, m) 3.60-3.82 (2 H, m), 4.02-4.11 (2 H, m), 7.14 (2 H, d, J=8), 7.23-7.29 (5 H, m) and 7.65 (2 H, d, J=8); m/z (ES) 490 (M^{+}+1).

d) 1-*tert*-Butyloxycarbonyl-4-fluoro-4-[3-tosyloxy-(2-phenyl)propyl]piperidine

The *title compound* (1.08 g, 43%) was prepared from the product of the preceding step (2.51 g, 5.13 mmol) following a similar method to that described for Example 2, step b. δ_H (250 MHz, $CDCl_3$) 1.17-1.80 (13 H, m) 1.86-2.09 (2 H, m), 2.43 (3 H, s), 2.87-3.04 (2 H, m), 3.16-3.28 (1 H, m),

3.72-3.92 (2 H, m), 4.01 (1 H, dd, J=10 and 7), 4.11 (1 H, dd, J=10 and 7), 7.08-7.12 (2 H, m), 7.22-7.30 (5 H, m) and 7.61-7.65 (2 H, m); m/z (ES) 492 (M^{+}+1).

e) 4-Fluoro-4-[3-fluoro-(2-phenyl)propyl]piperidine

A solution of the product of the previous step (1.00 g, 2.03 mmol) and tetrabutylammonium (triphenylsilyl)difluorosilicate (5.49 g, 10.2 mmol) in dry acetonitrile (30 ml) was refluxed under nitrogen for 64 hours. The mixture was cooled and solvent was removed by evaporation. The residues were triturated with 50% ethyl acetate-hexane and the mixture was filtered. The filtrate was concentrated and partly purified by flash column chromatography on silica, eluting with 15% ethyl acetate-hexane, to give crude 1-*tert*-butyloxycarbonyl-4-fluoro-4-[3-fluoro-(2-phenyl)propyl]piperidine. The material was dissolved in dichloromethane (4 ml) and trifluoroacetic acid (2 ml) was added. After standing at room temperature for 1.5 hours, solvent and excess acid were removed by evaporation. The residue was dissolved in aqueous sodium hydroxide (1 M, 15 ml) and extracted with dichloromethane (4 x 10 ml). The extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated. Preparative thin layer chromatography on silica, eluting with 90:9:1 dichloromethane-methanol-ammonia, gave the title compound (0.0421 g, 9%) as a colourless oil. δ_H (250 MHz, $CDCl_3$) 1.23-1.85 (4 H, m), 1.97-2.22 (2 H, m), 2.76-2.92 (4 H, m), 3.22-3.34 (1 H, m), 4.52 (2 H, dd, J=47 and 6) and 7.21-7.46 (5 H, m); m/z (ES) 240 (M^{+}+1).

f) 4-Fluoro-4-[3-fluoro-(2-phenyl)propyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine.

The *title compound free base* (0.024 g, 29%) was prepared from Intermediate 1 and the product of the preceding step following a similar method to that described for Example1, step d. Analytically pure material (2 mg) was isolated by preparative high performance liquid

chromatography. δ_H (360 MHz, $CDCl_3$) 1.25-2.38 (10 H, m), 2.40-2.50 (2 H, m), 2.60-2.76 (2 H, m), 2.77 (2 H, t, J=5), 3.12-3.26 (1 H, m), 4.45 (2 H, dd, J=47 and 6), 7.14 (2 H, dd, J=8 and 2), 7.22-7.26 (3 H, m), 7.30-7.34 (2 H, m), 7.46 (1 H, d, J=9), 7.53 (1 H, d, J=2), 8.30 (1 H, s) and 8.45 (2 H, s); m/z (ES) 464 (M^{+}+1).

EXAMPLE 14

4-Fluoro-4-[2-(4-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. Hydrogen Oxalate.

a) 1-*tert*-Butoxycarbonyl-4-fluoro-[2-(4-fluorophenyl)ethynyl]piperidine

A mixture of 1-*tert*-butoxycarbonyl-4-ethynyl-4-fluoropiperidine (1 g, 4.4 mmol) and 4-fluoroiodobenzene (610 µl, 5.3 mmol) in N,N-diethylamine (20 ml) was flushed with nitrogen for 15 mins, then palladium bis(triphenylphosphine)chloride (150 mg, 0.2 mmol) and copper (I) iodide (42 mg, 0.2 mmol) added. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 hours, then evaporated. The residue was treated with water (50 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic solutions were washed with water (1 x 50 ml), brine (1 x 20 ml), dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, ethyl acetate-hexane 1:9) gave 1.3 g (80%) of the *title compound*: δ_H (360MHz, $CDCl_3$) 1.47 (9H, s), 2.01-2.08 (4H, m), 3.51-3.64 (4H, m), 7.00-7.05 (2H, m), 7.42-7.46 (2H, m).

b) 1-*tert*-Butoxycarbonyl-4-fluoro-4-[2-(4-fluorophenyl)ethyl]piperidine

A solution of 1-*tert*-butoxycarbonyl-4-fluoro-4-[2-(4-fluorophenyl)ethynyl]piperidine in methanol (20 ml) and glacial acid (1 ml) was hydrogenated over 10% Pd-C (0.5 g) at 50 psi for 5 hours. The catalyst was removed by filtration and the solvents removed under vacuum. The residue was dissolved in diethyl ether (20 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 x 15 ml), dried

($MgSO_4$) and concentrated to give the title product (430 mg, 43%) which was used in the next step without further purification; δ_H (360MHz, $CDCl_3$) 1.46 (9H, s), 1.48-1.67 (2H, m), 1.82-1.93 (4H, m), 2.68-2.73 (2H, m), 3.05-3.20 (2H, m), 3.90-3.99 (2H, m), 6.94-6.99 (2H, m), 7.11-7.15 (2H, m): m/z (ES) 326 (M^{+}+1).

c) <u>4-Fluoro-4-[2-(4-fluorophenyl)ethyl]piperidine</u>

A solution of the product from the preceding step (430 mg, 1.3 mmol) in a mixture of trifluoroacetic acid and dichloromethane (1:2, 9 ml) was allowed to stand at room temperature for 2 hours. Solvents were removed under vacuum, and the residue treated with saturated aqueous sodium hydrogen carbonate (20 ml) and the product was extracted with dichloromethane (3 x 15 ml). The combined organic solutions were dried ($MgSO_4$) and concentrated to give 290 mg (97%) of the *title compound*, which was used in the next step without further purification. δ_H (360MHz, $CDCl_3$) 1.52-1.71 (2H, m), 1.82-1.92 (4H, m), 2.68-2.73 (2H, m), 2.93-3.00 (4H, m), 6.94-6.99 (2H, m), 7.12-7.16 (2H, m); m/z (ES) 226 (M^{+}+1).

d) <u>4-Fluoro-4-[2-(4-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. Hydrogen Oxalate</u>

The title compound free base was prepared from Intermediate 1 and the product from the preceding step following a similar method to that described for Example 1, step d. The oxalate salt was prepared from ethanol-diethyl ether, mp 205°C. (Found: C, 62.38; H, 5.80; N, 12.66. $C_{26}H_{29}F_2N_5$ x $1.0C_2H_2O_4$ requires: C, 62.33; H, 5.79; N, 12.98%) δ_H (360MHz, DMSO-d_6) 1.82-2.14 (8H, m), 2.64-2.69 (2H, m), 2.77 (2H, t, J=7.3Hz), 2.92-3.16 (4H, m), 3.28-3.40 (2H, m), 7.09 (2H, t, J=8.8Hz), 7.25-7.34 (4H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.8Hz), 9.03 (2H, s), 11.20 (1H, bs); m/z (ES) 450 (M^{+}+1).

Examples 15-21 were prepared from Intermediate 4 and the appropriate aryl-iodide following a similar procedure to that described for Example 14 (steps a, b, c and d).

EXAMPLE 15

4-Fluoro-4-(2-phenylethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 1.0 Hydrogen Oxalate

The oxalaté salt was prepared from ethanol-diethyl ether, mp 212°C. (Found: C, 64.05; H, 6.13; N, 13.32. $C_{26}H_{30}FN_5$ x $1.0C_2H_2O_4$ requires: C, 64.48; H, 6.18; N, 13.43%). δ_H (360MHz, DMSO-d_6) 1.84-2.14 (8H, m), 2.64-2.69 (2H, m), 2.77 (2H, t, J=7.4Hz), 2.94-3.12 (4H, m), 3.28-3.40 (2H, m), 7.16-7.34 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.9Hz), 9.03 (2H, s), 11.20 (1H, bs); m/z (ES) 432 (M^++1).

EXAMPLE 16

4-Fluoro-4-[2-(2-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 1.7 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether. mp 144°C. (Found: C, 58.72; H, 5.66; N, 11.33. $C_{26}H_{29}F_2N_5$ x $1.7C_2H_2O_4$ requires: C, 58.60; H, 5.42; N, 11.62%). δ_H (360MHz, DMSO-d_6) 1.84-2.14 (8H, m), 2.69-2.73 (2H, m), 2.75-2.79 (2H, t, J=7.4Hz), 3.00-.310 (4H, m), 3.36-3.44 (2H, m), 7.11-7.16 (2H, m), 7.23-7.29 (1H, m), 7.30-7.38 (4H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.9Hz), 9.03 (2H, s), 11.20 (1H, bs); m/z (ES) 450 (M^++1).

EXAMPLE 17

4-Fluoro-4-[2-(2-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. 1.3 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether, mp. 98°C. (Found: C, 61.21; H, 5.87; N, 12.38. $C_{27}H_{32}FN_5O$ x $1.3C_2H_2O_4$ requires: C, 61.44; H, 6.03; N, 12.10%). δ_H (360MHz, DMSO-d_6) 1.78-2.15 (8H, m), 2.60-

2.65 (2H, m), 2.78 (2H, t, J=7.2Hz), 3.00-3.18 (4H, m), 3.34-3.44 (2H, m), 3.77 (3H, s), 6.86 (1H, t, J=7.4Hz), 6.94 (1H, d, J=7.8Hz), 7.14-7.20 (2H, m), 7.31-7.35 (2H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.9Hz), 9.02 (2H, s), 11.20 (1H, bs); m/z (ES) 462 (M^++1).

EXAMPLE 18

4-Fluoro-4-[2-(2-thienyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine 1.5 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether, mp 211°C. (Found: C, 56.44; H, 5.50; N, 12.46. $C_{24}H_{28}FN_5S$ x $1.5C_2H_2O_4$ requires: C, 56.63; H, 5.46; N, 12.23%). δ_H (360MHz, DMSO-d_6) 1.88-2.16 (8H, m), 2.74-2.79 (2H, m), 2.87-2.93 (2H, m), 2.95-3.12 (4H, m), 3.26-3.40 (2H, m), 6.90-6.95 (2H, m), 7.31-7.34 (3H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, s), 9.03 (2H, s), 11.20 (1H, bs); m/z (ES) 438 (M^+ +1).

EXAMPLE 19

4-[2-(2-Cyanophenyl)ethyl]-4-fluoro-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine 1.4 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether, mp 98°C. (Found: C, 61.42; H, 5.66; N, 14.32. $C_{27}H_{29}FN_6$ x $1.4C_2H_2O_4$ requires: C, 61.43; H, 5.50; N, 14.42%). δ_H (360MHz, DMSO-d_6) 1.88-2.20 (8H, m), 2.72-2.84 (2H, m), 2.84-2.96 (2H, m), 3.00-3.20 (4H, m), 3.34-3.47 (2H, m), 7.32-7.35 (2H, m), 7.42 (1H, t, J=7.5Hz), 7.49-7.55 (2H, m), 7.65 (1H, t, J=7.3Hz), 7.78-7.82 (2H, m), 9.03 (2H, s), 11.21 (1H, bs); m/z (ES) 457 (M^++1).

EXAMPLE 20

4-Fluoro-4-[2-(3-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine 1.5 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether, mp 164°C. (Found: C, 60.77; H, 5.96; N, 11.65. $C_{27}H_{32}FN_5O$ x $1.5C_2H_2O_4$

requires: C, 60.39; H, 5.91; N, 11.74%). δ_H (360MHz, DMSO-d_6) 1.86-2.18 (8H, m), 2.61-2.67 (2H, m), 2.78 (2H, t, *J*=7.3Hz), 3.00-3.18 (4H, m), 3.26-3.48 (2H, m), 3.73 (3H, s), 6.75 (1H, d, *J*=8.4Hz), 6.80 (2H,m), 7.19 (1H, t, J=8.2 and 8.0Hz), 7.31-7.35 (2H, m), 7.50 (1H, d, *J*=8.6Hz), 7.81 (1H, d, *J*=1.9Hz), 9.03 (2H, s), 11.21 (1H, bs); m/z (ES) 462 (M^++1).

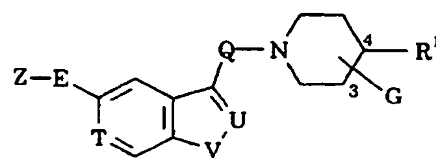
EXAMPLE 21

4-Fluoro-4-[2-(3-thienyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine 1.1 Hydrogen Oxalate

The oxalate salt was prepared from ethanol-diethyl ether. mp 208°C. (Found: C, 58.89; H, 5.81; N, 12.92. $C_{24}H_{28}FN_5S$ x $1.1C_2H_2O_4$ requires: C, 58.64; H, 5.67; N, 13.05%). δ_H (360MHz, DMSO-d_6) 1.98-2.18 (8H, m), 2.66-2.71 (2H, m), 2.77 (2H, t, *J*=7.4Hz), 2.94-3.16 (4H, m), 3.28-3.41 (2H, m), 7.02 (1H, d, *J*=4.9Hz), 7.20 (1H, s), 7.30-7.34 (2H, m), 7.44 (1H, dd, *J*=4.9 and 2.9Hz), 7.50 (1H, d, *J*=8.6Hz), 7.81 (1H, d, *J*=1.7Hz), 9.03 (2H, s), 11.22 (1H, bs); m/z (ES) 438 (M^++1).

CLAIMS:

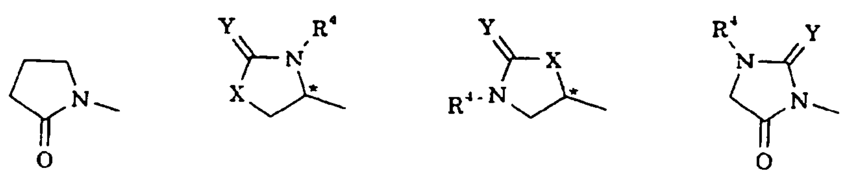
1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Z represents hydrogen, halogen, cyano, nitro, trifluoromethyl, $-OR^5$, $-OCOR^5$, $-OCONR^5R^6$, $-OCH_2CN$, $-OCH_2CONR^5R^6$, $-SR^5$, $-SOR^5$, $-SO_2R^5$, $-SO_2NR^5R^6$, $-NR^5R^6$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, or a group of formula (Za), (Zb), (Zc) or (Zd):



(Za) (Zb) (Zc) (Zd)

in which the asterisk * denotes a chiral centre; or

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

X represents oxygen, sulphur, -NH- or methylene;

Y represents oxygen or sulphur;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

U represents nitrogen or C-R^2;

V represents oxygen, sulphur or N-R^3;

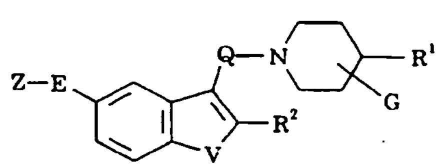
G is attached at position 3 or 4 of the piperidine ring and represents halogen or C_{1-6} alkoxy;

R^1 represents C_{3-6} alkenyl, C_{3-6} alkynyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

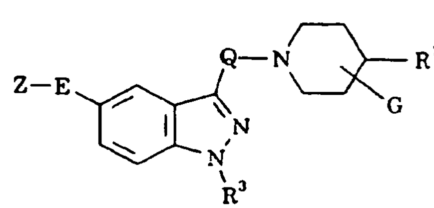
R^2, R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl; and

R^5 and R^6 independently represent hydrogen, C_{1-6} alkyl, trifluoromethyl, phenyl, methylphenyl, or an optionally substituted aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl group; or R^5 and R^6, when linked through a nitrogen atom, together represent the residue of an optionally substituted azetidine, pyrrolidine, piperidine, morpholine or piperazine ring.

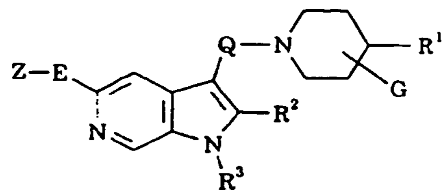
2. A compound according to claim 1 of formula IA, IB or IC:



(IA)



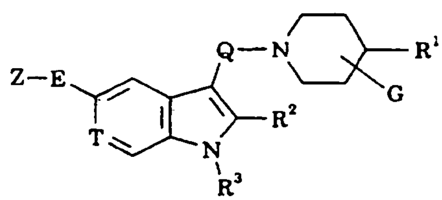
(IB)



(IC)

wherein Z, E, Q, V, G, R^1, R^2 and R^3 are as defined in claim 1.

3. A compound according to claim 1 of formula ID:



(ID)

wherein Z, E, Q, T, G, R^1, R^2 and R^3 are as defined in claim 1.

4. 4-Benzyl-4-fluoro-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-[2-(3-fluorophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-(3-fluorobenzyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-(2-fluorobenzyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-benzyl-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-benzyl-4-methoxy-1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]piperidine;

4-(2-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(3-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(4-fluorobenzyl)-4-methoxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-fluoro-4-[2-(trifluoromethyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(N,N-dimethylaminosulfonyl)benzyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-(2-phenylpropyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[3-fluoro-(2-phenyl)propyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(4-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-(2-phenylethyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-fluorophenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(2-thienyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-[2-(2-cyanophenyl)ethyl]-4-fluoro-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

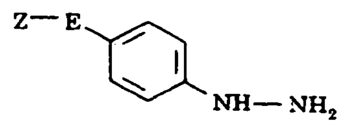
4-fluoro-4-[2-(3-methoxyphenyl)ethyl]-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

4-fluoro-4-[2-(3-thienyl)ethyl]-1-{3-[5-(1.2.4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine;

and salts and prodrugs thereof.

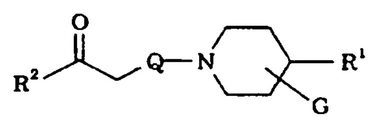
5. A process for producing a compound according to claim 1 which comprises:

(A) when T represents CH, U represents C-R^2 and V represents N-R^3 in the compound of formula I, reacting a compound of formula III:



(III)

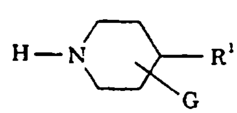
wherein Z and E are as defined in claim 1, with a compound of formula IV, or a carbonyl-protected form thereof:



(IV)

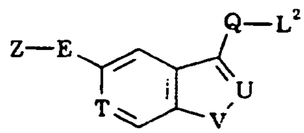
wherein Q, G, R^1 and R^2 are as defined in claim 1; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3;

(B) reacting a compound of formula VII



(VII)

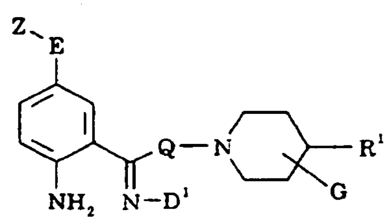
wherein Q, G, R^1 and R^2 are as defined in claim 1, with a compound of formula VIII:



(VIII)

wherein Z, E, Q, T, U and V are as defined in claim 1, and L^2 represents a suitable leaving group;

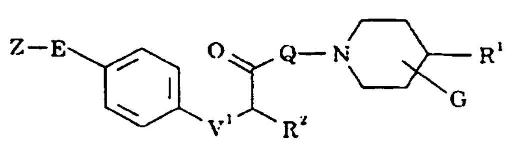
(C) when U represents nitrogen and V represents N-R^3 in the compound of formula I, cyclising a compound of formula X:



(X)

wherein Z, E, Q, G and R^1 are as defined in claim 1, and D^1 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3;

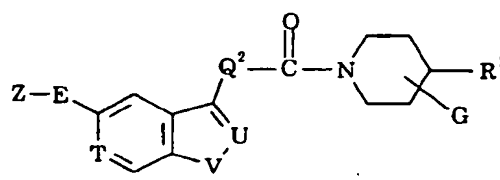
(D) when T represents CH, U represents C-R^2 and V represents oxygen or sulphur in the compound of formula I, cyclising a compound of formula XIII:



(XIII)

wherein Z, E, Q, G, R^1 and R^2 are as defined in claim 1, and V^1 represents oxygen or sulphur;

(E) reducing a compound of formula XVI:



(XVI)

wherein Z, E, T, U, V, G and R^1 are as defined in claim 1, and $-Q^2-CH_2-$ corresponds to the moiety Q as defined in claim 1; or

(F) elaborating a compound of formula I into a further compound of formula I.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, or pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof, and a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof, for use in a method of treatment of the human or animal body.

8. A compound according to claim 7 for use in the treatment of migraine.

9. The use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof, in the manufacture of a medicament for the treatment of a clinical condition for which a selective agonist of 5-HT_{1D_α} receptors is indicated.

10. A method of treatment of a subject suffering from a clinical condition for which a selective agonist of 5-HT_{1D_α} receptors is indicated, which comprises administering to that subject a therapeutically effective amount of a compound according to any one of claims 1 to 4 or a therapeutically acceptable salt or therapeutically acceptable prodrug thereof.

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/GB 96/02765

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 C07D409/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 21627 A (MERCK SHARP & DOHME LTD.) 29 September 1994 see claims ---	1-10
A	WO 94 02477 A (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see claims ---	1-10
P,A	WO 96 04274 A (MERCK SHARP & DOHME LTD.) 15 February 1996 see claims -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 1997	28.01.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

INTERNATIONAL SEARCH REPORT

Intern: ıl Application No
PCT/GB 96/02765

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9421627	29-09-94	AU-A-	6215594	11-10-94
		US-A-	5576336	19-11-96
WO-A-9402477	03-02-94	AU-B-	672802	17-10-96
		AU-A-	4578593	14-02-94
		CA-A-	2138649	03-02-94
		EP-A-	0651749	10-05-95
		JP-T-	7509452	19-10-95
		US-A-	5567726	22-10-96
WO-A-9604274	15-02-96	AU-A-	3182495	04-03-96